EPA Registration Number 73049-460 Vol 1

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF CHEMICAL SAFETY AND POLUTION PREVENTION/OFFICE OF PESTICIDE PROGRAMS

MEMORANDUM

DATE: 20 March 2012

SUBJECT: Science Review in Support of the Registration of S-Abscisic Acid TGAI, a Technical Grade Active Ingredient (TGAI) Product Containing 97.7% S-Abscisic Acid, As Its Active Ingredient. Review of Storage Stability and Corrosion Characteristics Studies.

Decision Number:	458538
DP Number:	399368
EPA File Symbol Number:	73049-460
Chemical Class:	Biochemical
PC Code:	272000
CAS Number:	14375-45-2
Tolerance Exemptions:	Pending
MRID Numbers:	48674901

FROM: Russell S. Jones, Ph.D., Senior Scientist
Biochemical Pesticides Branch
Biopesticides & Pollution Prevention Division (7511P)

3/20/2012

TO: Chris Pfeifer, Regulatory Action Leader
Biochemical Pesticides Branch
Biopesticides & Pollution Prevention Division (7511P)

ACTION REQUESTED

Valent Biosciences Corp. submitted a combined Storage Stability and Corrosion Characteristics study in support of the registration of S-Abscisic Acid Technical Grade Active Ingredient (EPA Reg. No. 73049-460). The studies were submitted in fulfillment of a condition of registration for the subject product.

S-Abscisic Acid
PC Code: 272000
Product chemistry: Storage Stability and Corrosion Characteristics

DP Numbers: 399368
EPA File Symbol No.: 73049-460

STUDY SUMMARIES

The test substance is identified as S-Abscisic Acid (S-ABA; Lot/Batch No. 185-471-W9-00) and was provided to the analytical laboratory (PTRL West, Inc., Hercules, CA) by Valent Biosciences Corporation (Libertyville, IL), the study sponsor. The substance was stored in polyethylene bags at room temperature until used in the study. The reference substance (99.7% S-ABA; Valent Batch No. 030806D1) was stored frozen when not in use. Samples were analyzed by High-Performance Liquid Chromatography (HPLC) equipped with a Diode Array Detector.

Details of the analytical methods, equipment and solvents may be found in MRID 48674901, pp. 11-17. Linearity of the standard curve was confirmed with correlation coefficients all ≥ 0.998. The accuracy of the method was confirmed with magnitudes of the relative errors being $\leq 4.67\%$. The method is precise with th4e relative standard deviation for each analysis $\leq 0.76\%$. (see MRID 48674901, Appendix C for details). Representative chromatograms are presented in MRID 48674901, pp. 23-30.

The storage stability of S-ABA Technical Grade Active Ingredient was tested for 12 months, with subsamples analyzed at Time 0, 3, 6, 9, and 12 months storage at ambient temperature in polyethylene bags. The percentage active ingredient at Time 0 was 98.14% and it declined to 97.05% after 12 months storage, a decline of only 1.1%. The results of the HPLC analyses may be found in MRID 48674901, Appendix D.

Corrosion characteristics were evaluated by visual inspection. No signs of corrosion were observed in the commercial packaging after 12 months of storage at ambient temperature. Corrosion characteristics data are presented in MRID 48674901, Table III, p. 22.

CLASSIFICATION: ACCEPTABLE, no additional data are required.

NO DERs WERE WRITTEN FOR THIS REVIEW

cc: R. S. Jones, C. Pfeifer, BPPD Science Review File, IHAD/ARS
Russell S. Jones, Ph.D., FT, PY-S: 03/20/2012

DATA PACKAGE BEAN SHEET

Date: 01-Mar-2012

Decision #: 458538
DP #: (399368)
NON PRIA
Parent DP #:
Submission #: 907713
E-Sub #:

* * * Registration Information * * *

Registration: 73049-460 - S-ABSCISIC ACID, TECHNICAL GRADE ACTIVE INGREDIEN

Company: 73049 - VALENT BIOSCIENCES CORPORATION

Risk Manager: RM 91 - Linda Hollis - (703) 308-8733 Room# PY1 S-8761

Risk Manager Reviewer: Jay Pfeifer JPFEIFER

Sent Date: 30-Nov-2011 Calculated Due Date: 19-Mar-2012 Edited Due Date:

Type of Registration: Product Registration - Section 3

Action Desc: (570) CONDITIONAL REGISTRATION FOLLOW-UP;DATA REQUIRED;REQUIRES RD REVII

Ingredients: 272000, Abscisic acid(97.7%)

* * * Data Package Information * * *

Expedite: ○ Yes ● No Date Sent: 01-Mar-2012 Due Back:

DP Ingredient: 272000, Abscisic acid

DP Title: SS & CC

CSF Included: ○ Yes ● No Label Included: ○ Yes ● No Parent DP #:

Assigned To		Date In	Date Out		
Organization:	BPPD / BPB	06-Mar-2012		Last Possible Science Due Date:	09-Jan-2012
Team Name:	RM 91	06-Mar-2012		Science Due Date:	
Reviewer Name:	Jones, Russell	06-Mar-2012		Sub Data Package Due Date:	
Contractor Name:					

* * * Studies Sent for Review * * *

Printed on Page 2

* * * Additional Data Package for this Decision * * *

No Additional Data Packages

* * * Data Package Instructions * * *

Review for Acceptability: SS & CC

Non-PRIA

DP#: (399368) *** Studies Sent for Review *** Decision#: (458538)

48674901		Schick, M. (2011) Physical Properties: Storage Stability and Corrosion Characteristics of S-Abscisic Acid. Project Number: 2048W 2048W/001. Unpublished study prepared by PTRL West, Inc. 52p.	830.6317/Storage stability	Pass (23-Dec-2011)
48674901		Schick, M. (2011) Physical Properties: Storage Stability and Corrosion Characteristics of S-Abscisic Acid. Project Number: 2048W 2048W/001. Unpublished study prepared by PTRL West, Inc. 52p.	830.6320/Corrosion characteristics	Pass (23-Dec-2011)

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

December 02, 2011

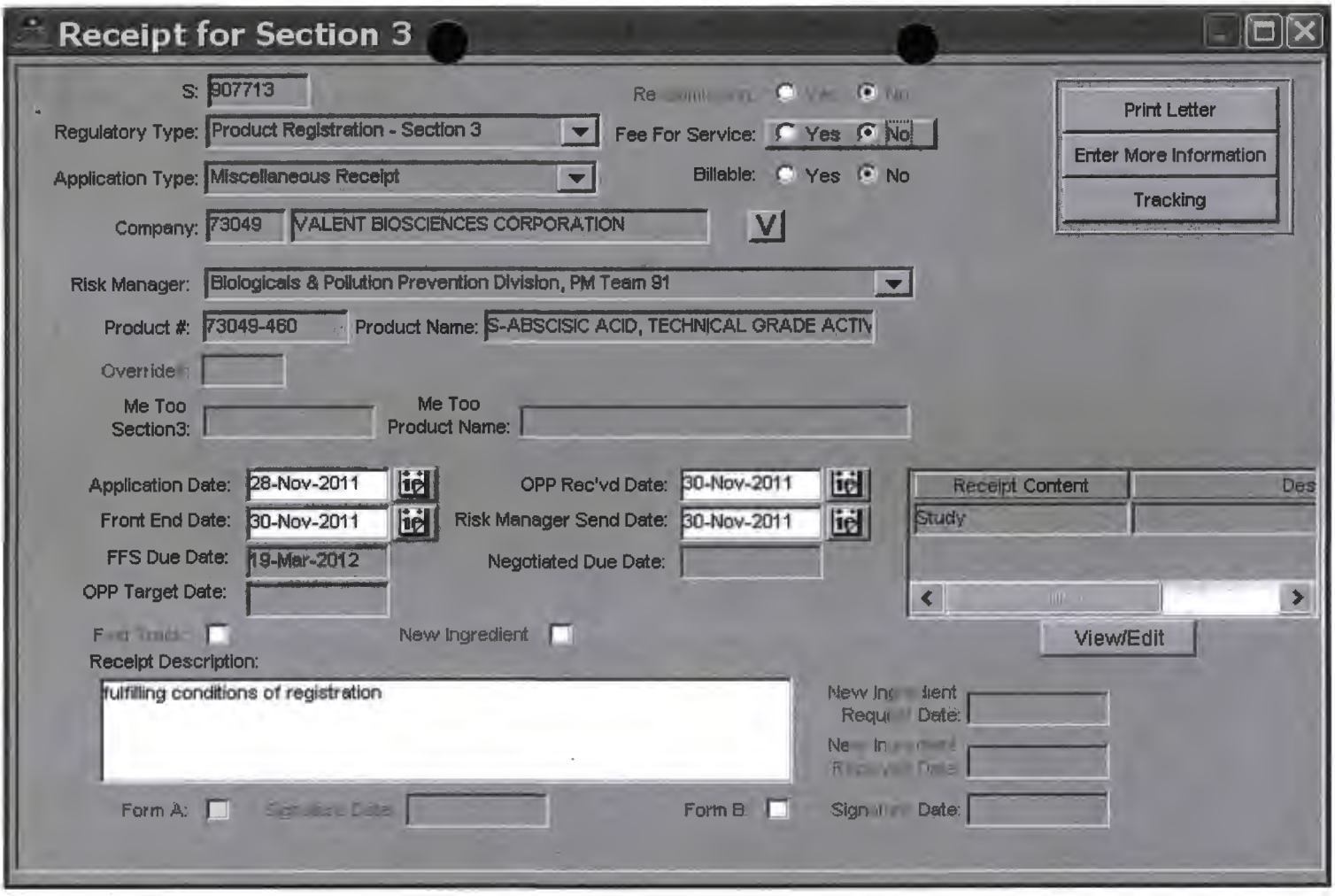
OFFICE OF CHEMICAL SAFETY
AND POLLUTION PREVENTION

VALENT BIOSCIENCES CORPORATION
870 TECHNOLOGY WAY, SUITE 100
LIBERTYVILLE, IL 60048-6316

Report of Analysis for Compliance with PR Notice 86-5

Thank you for your submittal of 30-NOV-11. Our staff has completed a preliminary analysis of the material. The results are provided as follows:

Your submittal was found to be in full compliance with the standards for submission of data contained in PR Notice 86-5. A copy of your bibliography is enclosed, annotated with Master Record ID's (MRIDs) assigned to each document submitted. Please use these numbers in all future references to these documents. Thank you for your cooperation. If you have any questions concerning this data submission, please raise them with the cognizant Product Manager, to whom the data have been released.



7 Recd 12/9/14 MB

VALENT BIOSCIENCES® CORPORATION

870 TECHNOLOGY WAY
LIBERTYVILLE, IL 60048 USA - 800-323-9597

48674900

November 28, 2011

Document Processing Desk
Office of Pesticide Programs (7504C)
U.S. Environmental Protection Agency
Room 266A, Crystal Mall 2
1921 Jefferson Davis Highway
Arlington, VA 22202

Attention: Chris Pfeifer
Regulatory Action Leader
Biochemical Pesticides Branch
Biopesticides and Pollution Prevention Division (7511P)
U.S. Environmental Protection Agency

Subject: Valent BioSciences Corp. (EPA Reg. No. 73049-460):
Fulfilling conditions of Section-3 registration of S-Abscisic Acid TGAI.

The following submission is fulfilling conditions of registration for the plant growth regulator S-Abscisic Acid TGAI (EPA Registration No. 73049-460).

A condition of registration for the biochemical pesticide S-Abscisic Acid TGAI (EPA Registration No. 73049-460) was to submit studies for the stability and corrosion characteristics for the MP (Manufacturing Use Product). The study guideline numbers and the report numbers being submitted are listed in the table below.

Guideline	Data Requirement	Report Number, (issue date)
830.6317	Storage Stability	Report #: PTRL 2048W-001, (June 22, 2011)
830.6320	Corrosion Characteristics	Report #: PTRL 2048W-001, (June 22, 2011)

This submission contains three (3) copies of the single report listed in the table above and two (2) copies of that final printed label.

Also included within this submission is a transmittal document that lists the one (1) new study being submitted.

VALENT BIOSCIENCES CORPORATION

This Submission is organized as follows:

Cover Letter
Form 8570-1 EPA Pesticide Registration Application form
Transmittal Document (listing 1 new study submitted)
Two copies of the Final Printed Label
Three copies of the submitted Study

Please contact me at (847)-968-4726 (or thomas.bade@valentbiosciences.com) if I can be of any assistance during the review of this application.

Sincerely,

Thomas Bade Ph.D.
Regulatory Manager
Valent BioSciences

Transmittal Document

Submitter: Valent BioSciences Corp.
879 Technology Way
Libertyville, IL 60048

Regulatory Action: Fulfilling Requirements of Section 3 Registration of S-ABA TGAI (Reg No. 73049-460)

Transmittal Date: October 3, 2011

Listing of Studies Submitted:

Document 1

Title: Physical Properties: Storage Stability and Corrosion Characteristics of S-Abscisic Acid
Data requirements: OPPTS 830.6317, 830.6320
Study Date: June 22, 2011
Performing Laboratory: PTRL West, Inc.
625-B Alfred Nobel Dr.
Hercules, CA 94547
Report ID: 2048W-001

MRID No.: **48674901**

Company Official: Signature

Company Name: Valent BioSciences Corporation

Company Contact: Thomas Bade Ph.D. 847-968-4726
Phone

Please read instructions on reverse before completing form. Form Approved. OMB No. 2070-0060

Print Form

United States
Environmental Protection Agency
Washington, DC 20460

- [ ] Registration
- [ ] Amendment
- [x] Other

OPP Identifier Number

Application for Pesticide - Section I

1. Company/Product Number	2. EPA Product Manager	3. Proposed Classification
Valent BioSciences, EPA # 73049-460	Linda Hollis	[x] None [ ] Restricted
4. Company/Product (Name) Valent BioSciences / S-Abscisic acid TGAI	**PM#** (91)	

5. Name and Address of Applicant *(Include ZIP Code)*

Valent BioSciences Corp.
870 Technology Way
Libertyville IL, 60048

[ ] *Check if this is a new address*

6. Expedited Review. In accordance with FIFRA Section 3(c)(3)(b)(i), my product is similar or identical in composition and labeling to:

EPA Reg. No. _____

Product Name _____

Section - II

- [ ] Amendment - Explain below.
- [ ] Resubmission in response to Agency letter dated _____
- [ ] Notification - Explain below.
- [x] Final printed labels in response to Agency letter dated July 25, 2011
- [ ] "Me Too" Application.
- [x] Other - Explain below.

Explanation: Use additional page(s) if necessary. (For section I and Section II.)

Fulfilling conditions of Registration of Abscisic acid TGAI (73049-460); Submit Storage Stability (830.6317) and Corrosion Characteristics (830.6320) study report,
AND Submission of Final Printed Label, Amended TGAI Approval July 25, 2011.

Section - III

1. Material This Product Will Be Packaged In:

Child-Resistant Packaging	Unit Packaging	Water Soluble Packaging	2. Type of Container
[ ] Yes* [ ] No	[ ] Yes [ ] No	[ ] Yes [ ] No	[ ] Metal [ ] Plastic [ ] Glass [ ] Paper [ ] Other (Specify) _____
* *Certification must be submitted*	If "Yes" Unit Packaging wgt. / No. per container	If "Yes" Package wgt / No. per container	

3. Location of Net Contents Information	4. Size(s) Retail Container	5. Location of Label Directions
[ ] Label [ ] Container		[ ] On Label [ ] On Labeling accompanying product

6. Manner in Which Label is Affixed to Product [ ] Lithograph [ ] Paper glued [ ] Stenciled [ ] Other _____

Section - IV

1. Contact Point *(Complete items directly below for identification of individual to be contacted, if necessary, to process this application.)*

Name	Title	Telephone No. (Include Area Code)
Thomas Bade P.hD.	Regulatory Manager	847-968-4726

Certification

I certify that the statements I have made on this form and all attachments thereto are true, accurate and complete. I acknowledge that any knowingly false or misleading statement may be punishable by fine or imprisonment or both under applicable law.

2. Signature	3. Title	6. Date Application Received (Stamped)
Thomas Bade	Regulatory Manager	
4. Typed Name Thomas Bade	**5. Date** 11/28/2011	

EPA Form 8570-1 (Rev. 8-94) Previous editions are obsolete. White - EPA File Copy (original) Yellow - Applicant Copy

S-ABSCISIC ACID

TECHNICAL GRADE ACTIVE INGREDIENT

FOR FORMULATION INTO PLANT GROWTH REGULATOR (PGR) PRODUCTS
FOR MANUFACTURING OR FORMULATION USE ONLY

Active Ingredient:	
S-Abscisic Acid	97.7% w/w
Other Ingredients	2.3% w/w
Total	100.0% w/w

EPA Reg. No.: 73049-460
EPA Est. No.: 081887-CHN-001

KEEP OUT OF REACH OF CHILDREN

CAUTION

FIRST AID	
If in Eyes:	• Hold eye open and rinse slowly and gently with water for 15-20 minutes. • Remove contact lenses, if present, after the first 5 minutes, then continue rinsing eye. • Call a poison control center or doctor for treatment advice.

HOT LINE NUMBER

Have the product container or label with you when calling a poison control center or doctor, or going for treatment. You may also call toll-free 1-800-892-0099 (24 hours) for emergency medical treatment and/or transport emergency information. For all other information, call 1-847-968-4700.

Manufactured By:

Sichuan Lomon Bio Technology Co., Ltd.
325 He Xiang Road,
Dayi County 611330, Chengdu,
Sichuan, China

PRECAUTIONARY STATEMENTS

HAZARDS TO HUMANS & DOMESTIC ANIMALS

CAUTION: Causes moderate eye irritation. Avoid contact with eyes or clothing. Wash thoroughly with soap and water after handling and before eating, drinking, chewing gum, using tobacco, or using the toilet. Mixers, loaders and handlers must wear the appropriate Personal Protective Equipment (PPE): long sleeved shirt and pants, shoes and socks, and protective eyewear. Remove and wash contaminated clothing before reuse.

ENVIRONMENTAL HAZARDS

Do not discharge effluent containing this product into lakes, streams, ponds, estuaries, oceans or other waters unless in accordance with the requirements of a National Pollutant Discharge Elimination Systems (NPDES) permit and the permitting authority has been notified in writing prior to discharge. Do not discharge effluent containing this product to sewer systems without previously notifying the local sewage treatment plant authority. For guidance contact your State Water Board or Regional Office of the EPA. Do not contaminate water when disposing of equipment washwaters or rinsate.

DIRECTIONS FOR USE

It is a violation of Federal law to use this product in a manner inconsistent with its labeling.

S-Abscisic Acid is intended for use in the formulation of Plant Growth Regulator (PGR) products, to be applied to field and container-grown plants to induce and regulate PGR responses.

This product may be used to formulate products for any additional uses not listed on the MP label if the formulator has complied with U.S. EPA data submission requirements regarding the support of such uses. Products made from this technical material will require registration with the U.S. Environmental Protection Agency (EPA).

STORAGE AND DISPOSAL

Do not contaminate water, food or feed by storage or disposal.

Pesticide Storage: Keep container tightly closed when not in use. Store product in a cool and dry place. Avoid extended storage conditions at temperatures above 25°C (77°F).

Net Contents: 4.4 g

Lot.: 11.06.11

STORAGE AND DISPOSAL (Cont'd)

Pesticide Disposal: To avoid wastes, use all material in this container according to label directions. If wastes cannot be avoided, offer remaining product to a waste disposal facility or pesticide disposal program (often such programs are run by state or local governments or by industry). Do not contaminate water when disposing of equipment washwater or rinsate. Improper disposal of unused pesticide, washwater or rinsate is a violation of federal law.

Container Disposal: Non-refillable container. Do not reuse or refill this container. Triple rinse container (or equivalent) promptly after emptying. Triple rinse as follows: Completely empty drum liner by shaking and tapping sides and bottom to loosen clinging particles. Empty residue into manufacturing equipment. Fill 1/4 full with water. Shake for 10 seconds. Pour rinsate into manufacturing equipment or a mix tank or store rinsate for later use or disposal. Drain for 10 seconds after the flow begins to drip. Repeat this procedure two more times. Then offer for recycling if available or puncture and dispose of in a sanitary landfill, or by incineration. Do not burn, unless allowed by state and local ordinances.

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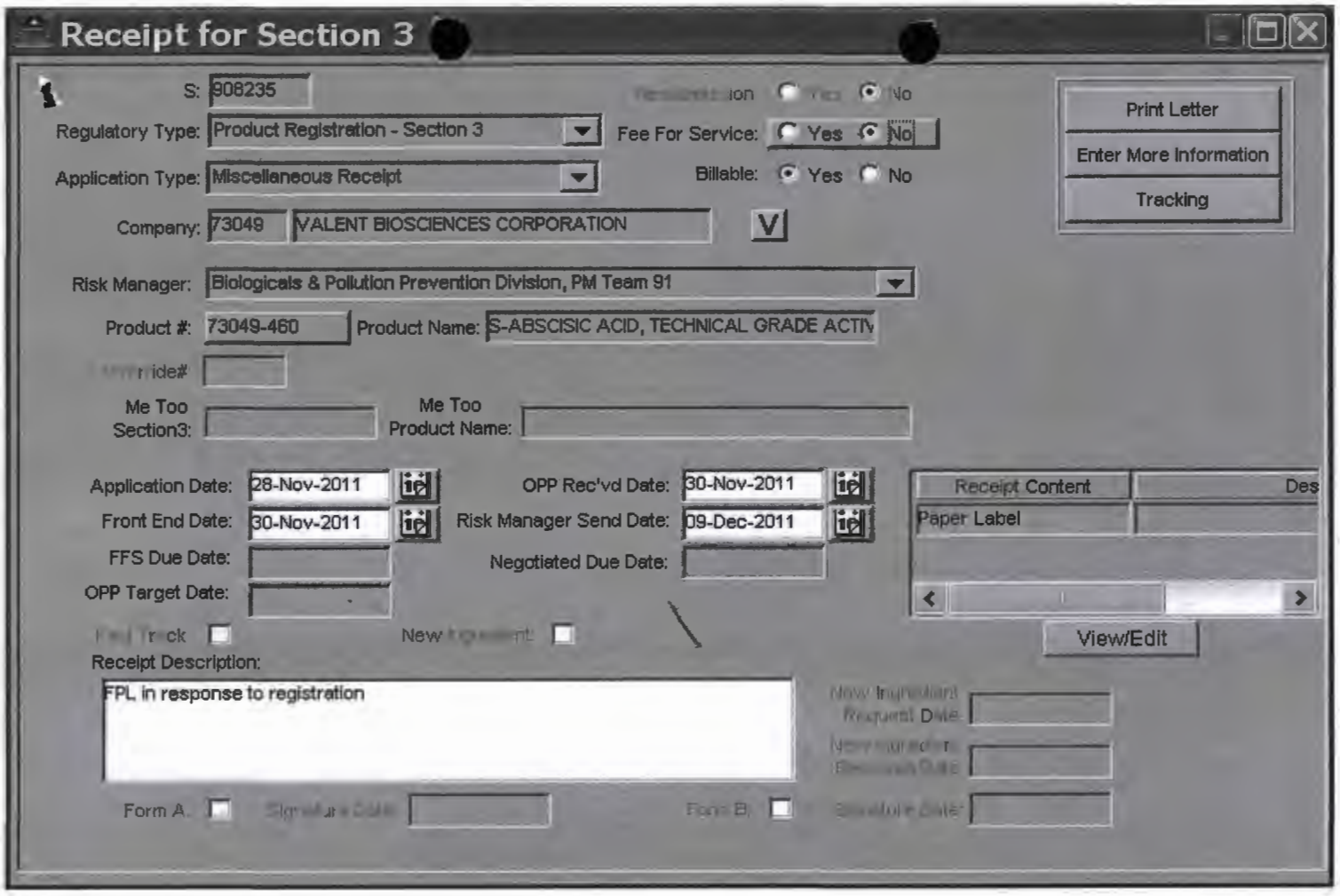
Warranty and Disclaimer Statement:
To the fullest extent permitted by law, seller makes no warranty, express or implied, of merchantability, fitness or otherwise concerning use of this product other than as indicated on the label. User assumes all risks of use, storage or handling not in strict accordance with accompanying directions.

Manufactured For:

VALENT BIOSCIENCES CORPORATION
870 Technology Way
Libertyville, IL 60048 U.S.A.
1-847-968-4700

04-6966/R4



458539

Completed 12/9/2011 SG

Recd 12/9/11 MB

VALENT BIOSCIENCES CORPORATION
870 TECHNOLOGY WAY
LIBERTYVILLE, IL 60048 USA - 800-323-9597

48674900

November 28, 2011

Document Processing Desk
Office of Pesticide Programs (7504C)
U.S. Environmental Protection Agency
Room 266A, Crystal Mall 2
1921 Jefferson Davis Highway
Arlington, VA 22202

Attention: Chris Pfeifer
Regulatory Action Leader
Biochemical Pesticides Branch
Biopesticides and Pollution Prevention Division (7511P)
U.S. Environmental Protection Agency

Subject: Valent BioSciences Corp. (EPA Reg. No. 73049-460):
Fulfilling conditions of Section-3 registration of S-Abscisic Acid TGAI.

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A condition of registration for the biochemical pesticide S-Abscisic Acid TGAI (EPA Registration No. 73049-460) was to submit studies for the stability and corrosion characteristics for the MP (Manufacturing Use Product). The study guideline numbers and the report numbers being submitted are listed in the table below.

Guideline	Data Requirement	Report Number, (issue date)
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830.6320	Corrosion Characteristics	Report #: PTRL 2048W-001, (June 22, 2011)

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VALENT BIOSCIENCES CORPORATION

This Submission is organized as follows:

Cover Letter
Form 8570-1 EPA Pesticide Registration Application form
Transmittal Document (listing 1 new study submitted)
Two copies of the Final Printed Label
Three copies of the submitted Study

Please contact me at (847)-968-4726 (or thomas.bade@valentbiosciences.com) if I can be of any assistance during the review of this application.

Sincerely,

Thomas Bade Ph.D.
Regulatory Manager
Valent BioSciences

Please read instructions on reverse before completing form.

Form Approved. OMB No. 2070-0060

Print Form

United States
Environmental Protection Agency
Washington, DC 20460

☐ Registration
☐ Amendment
☒ Other

OPP Identifier Number

Application for Pesticide - Section I

1. Company/Product Number	2. EPA Product Manager	3. Proposed Classification
Valent BioSciences, EPA # 73049-460	Linda Hollis	☒ None ☐ Restricted
4. Company/Product (Name)	**PM#**	
Valent BioSciences / S-Abscisic acid TGAI	(91)	

5. Name and Address of Applicant *(Include ZIP Code)*

Valent BioSciences Corp.
870 Technology Way
Libertyville IL, 60048

☐ *Check if this is a new address*

6. Expedited Review. In accordance with FIFRA Section 3(c)(3)(b)(i), my product is similar or identical in composition and labeling to:

EPA Reg. No. _____

Product Name _____

Section - II

☐ Amendment - Explain below.
☐ Resubmission in response to Agency letter dated _____
☐ Notification - Explain below.
☒ Final printed labels in response to Agency letter dated July 25, 2011
☐ "Me Too" Application.
☒ Other - Explain below.

Explanation: Use additional page(s) if necessary. (For section I and Section II.)

Fulfilling conditions of Registration of Abscisic acid TGAI (73049-460); Submit Storage Stability (830.6317) and Corrosion Characteristics (830.6320) study report,
AND Submission of Final Printed Label, Amended TGAI Approval July 25, 2011.

Section - III

1. Material This Product Will Be Packaged In:

Child-Resistant Packaging	Unit Packaging	Water Soluble Packaging	2. Type of Container
☐ Yes* ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Metal ☐ Plastic ☐ Glass ☐ Paper ☐ Other (Specify) _____
* *Certification must be submitted*	If "Yes" Unit Packaging wgt. / No. per container	If "Yes" Package wgt / No. per container	

3. Location of Net Contents Information	4. Size(s) Retail Container	5. Location of Label Directions
☐ Label ☐ Container		☐ On Label ☐ On Labeling accompanying product

6. Manner in Which Label is Affixed to Product ☐ Lithograph ☐ Paper glued ☐ Stenciled ☐ Other _____

Section - IV

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Thomas Bade P.hD.	Regulatory Manager	847-968-4726

Certification

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6. Date Application Received (Stamped)

2. Signature	3. Title
Thomas Bade	Regulatory Manager
4. Typed Name	**5. Date**
Thomas Bade	11/28/2011

EPA Form 8570-1 (Rev. 8-94) Previous editions are obsolete. White - EPA File Copy (original) Yellow - Applicant Copy

S-ABSCISIC ACID

TECHNICAL GRADE ACTIVE INGREDIENT

FOR FORMULATION INTO PLANT GROWTH REGULATOR (PGR) PRODUCTS FOR MANUFACTURING OR FORMULATION USE ONLY

Active Ingredient:	
S-Abscisic Acid	97.7% w/w
Other Ingredients	2.3% w/w
Total	100.0% w/w

EPA Reg. No.: 73049-460
EPA Est. No.: 081887-CHN-001

KEEP OUT OF REACH OF CHILDREN

CAUTION

FIRST AID	
If in Eyes:	• Hold eye open and rinse slowly and gently with water for 15-20 minutes. • Remove contact lenses, if present, after the first 5 minutes, then continue rinsing eye. • Call a poison control center or doctor for treatment advice.

HOT LINE NUMBER

Have the product container or label with you when calling a poison control center or doctor, or going for treatment. You may also call toll-free 1-800-892-0099 (24 hours) for emergency medical treatment and/or transport emergency information. For all other information, call 1-847-968-4700.

Manufactured By:

Sichuan Lomon Bio Technology Co., Ltd.
325 He Xiang Road,
Dayi County 611330, Chengdu,
Sichuan, China

PRECAUTIONARY STATEMENTS

HAZARDS TO HUMANS & DOMESTIC ANIMALS

CAUTION: Causes moderate eye irritation. Avoid contact with eyes or clothing. Wash thoroughly with soap and water after handling and before eating, drinking, chewing gum, using tobacco, or using the toilet. Mixers, loaders and handlers must wear the appropriate Personal Protective Equipment (PPE): long sleeved shirt and pants, shoes and socks, and protective eyewear. Remove and wash contaminated clothing before reuse.

ENVIRONMENTAL HAZARDS

Do not discharge effluent containing this product into lakes, streams, ponds, estuaries, oceans or other waters unless in accordance with the requirements of a National Pollutant Discharge Elimination Systems (NPDES) permit and the permitting authority has been notified in writing prior to discharge. Do not discharge effluent containing this product to sewer systems without previously notifying the local sewage treatment plant authority. For guidance contact your State Water Board or Regional Office of the EPA. Do not contaminate water when disposing of equipment washwaters or rinsate.

DIRECTIONS FOR USE

It is a violation of Federal law to use this product in a manner inconsistent with its labeling.

S-Abscisic Acid is intended for use in the formulation of Plant Growth Regulator (PGR) products, to be applied to field and container-grown plants to induce and regulate PGR responses.

This product may be used to formulate products for any additional uses not listed on the MP label if the formulator has complied with U.S. EPA data submission requirements regarding the support of such uses. Products made from this technical material will require registration with the U.S. Environmental Protection Agency (EPA).

STORAGE AND DISPOSAL

Do not contaminate water, food or feed by storage or disposal.

Pesticide Storage: Keep container tightly closed when not in use. Store product in a cool and dry place. Avoid extended storage conditions at temperatures above 25°C (77°F).

Net Contents:

Lot.:

Complies with EPA Accepted Labeling

Date: July 25, 2011

Reviewer: Sylvester George

STORAGE AND DISPOSAL (Cont'd)

Pesticide Disposal: To avoid wastes, use all material in this container according to label directions. If wastes cannot be avoided, offer remaining product to a waste disposal facility or pesticide disposal program (often such programs are run by state or local governments or by industry). Do not contaminate water when disposing of equipment washwater or rinsate. Improper disposal of unused pesticide, washwater or rinsate is a violation of federal law.

Container Disposal: Non-refillable container. Do not reuse or refill this container. Triple rinse container (or equivalent) promptly after emptying. Triple rinse as follows: Completely empty drum liner by shaking and tapping sides and bottom to loosen clinging particles. Empty residue into manufacturing equipment. Fill 1/4 full with water. Shake for 10 seconds. Pour rinsate into manufacturing equipment or a mix tank or store rinsate for later use or disposal. Drain for 10 seconds after the flow begins to drip. Repeat this procedure two more times. Then offer for recycling if available or puncture and dispose of in a sanitary landfill, or by incineration. Do not burn, unless allowed by state and local ordinances.

Non-refillable container. Do not reuse or refill this container. Triple rinse container (or equivalent) promptly after emptying. Triple rinse as follows: Completely empty drum contents into manufacturing equipment or a mix tank by shaking and tapping sides and bottom to loosen clinging particles. Fill container 1/4 full with water. Replace and tighten closures. Tip container on its side and roll it back and forth, ensuring at least one complete revolution, for 30 seconds. Stand the container on its end and tip it back and forth several times. Turn the container over onto its other end and tip it back and forth several times. Empty the rinsate into application equipment or a mix tank or store rinsate for later use or disposal. Repeat this procedure two more times. Then offer for recycling if available or puncture and dispose of in a sanitary landfill, or by incineration. Do not burn, unless allowed by state and local ordinances.

Warranty and Disclaimer Statement:

To the fullest extent permitted by law, seller makes no warranty, express or implied, of merchantability, fitness or otherwise concerning use of this product other than as indicated on the label. User assumes all risks of use, storage or handling not in strict accordance with accompanying directions.

Manufactured For:

VALENT BIOSCIENCES CORPORATION
870 Technology Way
Libertyville, IL 60048 U.S.A.
1-847-968-4700

04-6966/R4

S-ABSCISIC ACID

TECHNICAL GRADE ACTIVE INGREDIENT

FOR FORMULATION INTO PLANT GROWTH REGULATOR (PGR) PRODUCTS
FOR MANUFACTURING OR FORMULATION USE ONLY

Active Ingredient:	
S-Abscisic Acid	97.7% w/w
Other Ingredients	2.3% w/w
Total	100.0% w/w

EPA Reg. No.: 73049-460
EPA Est. No.: 081887-CHN-001

KEEP OUT OF REACH OF CHILDREN

CAUTION

FIRST AID	
If in Eyes:	• Hold eye open and rinse slowly and gently with water for 15-20 minutes. • Remove contact lenses, if present, after the first 5 minutes, then continue rinsing eye. • Call a poison control center or doctor for treatment advice.

HOT LINE NUMBER

Have the product container or label with you when calling a poison control center or doctor, or going for treatment. You may also call toll-free 1-800-892-0099 (24 hours) for emergency medical treatment and/or transport emergency information. For all other information, call 1-847-968-4700.

Manufactured By:

Sichuan Lomon Bio Technology Co., Ltd.
325 He Xiang Road,
Dayi County 611330, Chengdu,
Sichuan, China

PRECAUTIONARY STATEMENTS
HAZARDS TO HUMANS & DOMESTIC ANIMALS

CAUTION: Causes moderate eye irritation. Avoid contact with eyes or clothing. Wash thoroughly with soap and water after handling and before eating, drinking, chewing gum, using tobacco, or using the toilet. Mixers, loaders and handlers must wear the appropriate Personal Protective Equipment (PPE): long sleeved shirt and pants, shoes and socks, and protective eyewear. Remove and wash contaminated clothing before reuse.

ENVIRONMENTAL HAZARDS

Do not discharge effluent containing this product into lakes, streams, ponds, estuaries, oceans or other waters unless in accordance with the requirements of a National Pollutant Discharge Elimination Systems (NPDES) permit and the permitting authority has been notified in writing prior to discharge. Do not discharge effluent containing this product to sewer systems without previously notifying the local sewage treatment plant authority. For guidance contact your State Water Board or Regional Office of the EPA. Do not contaminate water when disposing of equipment washwaters or rinsate.

DIRECTIONS FOR USE

It is a violation of Federal law to use this product in a manner inconsistent with its labeling.

S-Abscisic Acid is intended for use in the formulation of Plant Growth Regulator (PGR) products, to be applied to field and container-grown plants to induce and regulate PGR responses.

This product may be used to formulate products for any additional uses not listed on the MP label if the formulator has complied with U.S. EPA data submission requirements regarding the support of such uses. Products made from this technical material will require registration with the U.S. Environmental Protection Agency (EPA).

STORAGE AND DISPOSAL

Do not contaminate water, food or feed by storage or disposal.

Pesticide Storage: Keep container tightly closed when not in use. Store product in a cool and dry place. Avoid extended storage conditions at temperatures above 25°C (77°F).

Net Contents:

Lot.:

STORAGE AND DISPOSAL (Cont'd)

Pesticide Disposal: To avoid wastes, use all material in this container according to label directions. If wastes cannot be avoided, offer remaining product to a waste disposal facility or pesticide disposal program (often such programs are run by state or local governments or by industry). Do not contaminate water when disposing of equipment washwater or rinsate. Improper disposal of unused pesticide, washwater or rinsate is a violation of federal law.

Container Disposal: Non-refillable container. Do not reuse or refill this container. Triple rinse container (or equivalent) promptly after emptying. Triple rinse as follows: Completely empty drum liner by shaking and tapping sides and bottom to loosen clinging particles. Empty residue into manufacturing equipment. Fill 1/4 full with water. Shake for 10 seconds. Pour rinsate into manufacturing equipment or a mix tank or store rinsate for later use or disposal. Drain for 10 seconds after the flow begins to drip. Repeat this procedure two more times. Then offer for recycling if available or puncture and dispose of in a sanitary landfill, or by incineration. Do not burn, unless allowed by state and local ordinances.

Non-refillable container. Do not reuse or refill this container. Triple rinse container (or equivalent) promptly after emptying. Triple rinse as follows: Completely empty drum contents into manufacturing equipment or a mix tank by shaking and tapping sides and bottom to loosen clinging particles. Fill container 1/4 full with water. Replace and tighten closures. Tip container on its side and roll it back and forth, ensuring at least one complete revolution, for 30 seconds. Stand the container on its end and tip it back and forth several times. Turn the container over onto its other end and tip it back and forth several times. Empty the rinsate into application equipment or a mix tank or store rinsate for later use or disposal. Repeat this procedure two more times. Then offer for recycling if available or puncture and dispose of in a sanitary landfill, or by incineration. Do not burn, unless allowed by state and local ordinances.

Warranty and Disclaimer Statement:

To the fullest extent permitted by law, seller makes no warranty, express or implied, of merchantability, fitness or otherwise concerning use of this product other than as indicated on the label. User assumes all risks of use, storage or handling not in strict accordance with accompanying directions.

Manufactured For:

VALENT BIOSCIENCES CORPORATION
870 Technology Way
Libertyville, IL 60048 U.S.A.
1-847-968-4700

04-6966/R4

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

Thomas Bade, Ph.D.
Valent BioSciences Corporation
870 Technology Way
Libertyville, IL 60048

JUL 25 2011

Subject: Valent BioSciences Corporation; S-Abscisic Acid, Technical Grade Active Ingredient, EPA Registration No. 73049-460
Application with Data to Amend the Manufacturing Process, Label and CSF; B680
D# 446993, Application Dated 3/23/11, PRIA Date 8/15/11

Dear Dr. Bade:

The amendment referred to above, submitted in connection with registration under FIFRA section 3(c)(7)(A), is acceptable provided that you:

1. Submit and/or cite all data required for registration/reregistration of your product under FIFRA section 3(c)(5) when the Agency requires all registrants of similar products to submit such data.

2. Submit two (2) copies of your final printed labeling before you release the product for shipment. Final printed labeling means the label or labeling of the product when distributed or sold. Clearly legible reproductions or photo reductions will be accepted for unusual labels, such as those silk-screened directly onto glass or metal containers or large bags or drum labels.

If these conditions are not complied with, the registration will be subject to cancellation in accordance with FIFRA section 6(b). Your release for shipment of the product bearing the amended labeling constitutes acceptance of these conditions.

If you have any questions contact Chris Pfeifer at 703-308-0031 or by email at: pfeifer.chris@epa.gov. A stamped copy of the label is enclosed for your records.

Sincerely,

Linda A. Hollis, Chief
Biochemical Pesticides Branch
Biopesticides and Pollution
Prevention Division (7511P)

Enclosure

CONCURRENCES								
SYMBOL ▶	7511P							
SURNAME ▶	PFEIFER							
DATE ▶	7/29/11							

S-Abscisic Acid, Technical Grade Active Ingredient (S-ABA, VBC-30054)

FOR FORMULATION INTO PLANT GROWTH REGULATOR (PGR) PRODUCTS

FOR MANUFACTURING OR FORMULATION USE ONLY

Active Ingredient	
S-Abscisic Acid	97.7% w/w
Other Ingredients	2.3% w/w
Total	100.0% w/w

KEEP OUT OF REACH OF CHILDREN
CAUTION

FIRST AID	
If in Eyes	• Hold eye open and rinse slowly and gently with water for 15-20 minutes. • Remove contact lenses, if present, after the first 5 minutes, then continue rinsing eye. • Call a poison control center or doctor for treatment advice.
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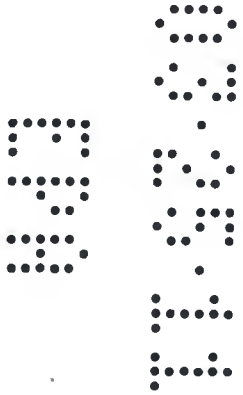
EPA Registration No. 73049-460
EPA Establishment No.

Valent BioSciences Corporation
870 Technology Way
Libertyville, IL 60048
1-847-968-4700

Net Content: 25 kg, 50 kg

ACCEPTED
JUL 25 2011
Under the Federal Insecticide, Fungicide, and Rodenticide Act, as amended, for the pesticide registered under EPA Reg. No. 73049-460



PRECAUTIONARY STATEMENTS

HAZARDS TO HUMANS & DOMESTIC ANIMALS

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DIRECTIONS FOR USE

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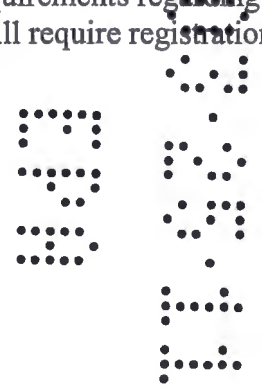

STORAGE AND DISPOSAL

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S-Abscisic Acid, Technical Grade Active Ingredient (S-ABA, VBC-30054)

FOR FORMULATION INTO PLANT GROWTH REGULATOR (PGR) PRODUCTS

FOR MANUFACTURING OR FORMULATION USE ONLY

Dangod 3/22/11

Active Ingredient	
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Total	100.0% w/w

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EPA Registration No. 73049-460
EPA Establishment No.

Valent BioSciences Corporation
870 Technology Way
Libertyville, IL 60048
1-847-968-4700

Net Content: 25 kg, 50 kg

PRECAUTIONARY STATEMENTS

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Warranty and Disclaimer Statement:
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Changed
3/22/11

BPPD Label Amendment Checklist
Fast Track ☐ and PRIA Actions B680 ☑ B73 ☐ &B90 ☐

EPA Reg. No.: 73049-460 **RAL: Chris Pfeifer** **Application Date: 3/25/11**

#	Check list Item	Yes	No
1.	**Application Form** (EPA Form 8570-1) - signed & complete, including package type? **If NO, stop!** Call applicant and have them correct application and resubmit.	√	
2.	**Final printed labeling** received for previous action? **If NO, stop!** E-mail applicant and request final printed labeling (FPL).	√	
3.	**Data and Data Matrix** present? (EPA Form 8570-35) A Data Matrix is not required for 100% repacks that have the same label uses as the parent product, and that derive their data from the formulator; nor is it required for minor amendments, which do not rely on data. In these cases, skip to Item 5.		√
a.	Using Selective Method (including the cite-all option under the Selective Method)? **If using Cite-all method only, skip to Item 4.**	√	
b.	Complete Data Matrix supporting both the product registration and the proposed amendment. Minimum Data Matrix for registration includes: Product specific Acute Toxicity and Product Chemistry data, plus Efficacy data for public health pests claimed on label.	√	
c.	Adequate product specific data?	√	
d.	Registered source used for active ingredient? **If YES, skip to Item 5. If NO or if use not supported by registered source, generic data is necessary.**	√	
e.	Data passed PR Notice 86-5 for formatting and MRID assignment?	√	
f.	Public copy of Data Matrix provided? (PRN 98-5)	√	
4.	**Certification with Respect to Citation of Data** present. (EPA Form 8570-34): See 40 CFR 152.80-98 and PR Notice 98-5. (If no data are required, a Certification with Respect to Citation of Data form isn't needed. This is often true for minor amendments.) NA ☐	√	
a.	Did applicant check a Method of Support?	√	
b.	General Offer to Pay checked for Cite-all Method or Cite-all under Selective Method?	√	
c.	Is the form signed and dated?	√	
d.	Check form and Data Matrix. Are Exclusive Use data cited from other sources?		√
	If YES, is the required authorization letter included in application? NA ☐		
5.	**Label(s) Review** **Date of Label Review: 7/12/11**		
a.	Label(s) in conformance with current *Label Review Manual* and appropriate REDS.	√	
b.	Labeling from Acute Toxicity, Product Chemistry, and Efficacy data for public health pests claimed on label.	√	
c.	Nominal concentration of active ingredient shown in ingredients statement.	√	
d.	Viability included as sub-statement of Ingredient Statement (if live microbial, i.e., cfu/gram). NA ☑		
e.	Storage and disposal instructions agree with container types listed on application form.	√	
f.	Unique Product Name for Same Company (Check OPPIN).	√	
g.	Does CSF list peanuts, tree nuts, milk, soybeans, eggs (including putrescent eggs), fish, crustacea, or wheat commodities? **If YES, RAL must evaluate label for compliance with 40 CFR 180.1071.**		√
h.	Does label bear "National Organic Program" (PR Notice 2003-1) or OMRI claims?		√
i.	If YES, National Organic Program or OMRI claims approved by Chris Pfeifer? NA ☑		
	Labeling is acceptable. Corrections or changes are NOT necessary.	√	
j.	Comments: The only change to the label from the last label review (2/10) was achange in the percentage active ingredient.		

BASIC CHECK LIST FOR CONFIDENTIAL STATEMENT OF FORMULAS (CSF)

Please note that if you have any questions at any point, especially with chemical or microbial names, consult with a chemist/ product characterization scientist. It may be helpful to make a copy of the CSF for marking comments, questions, and needed corrections. Upon completion of this form, consult the above scientists. And have them check over the CSF along with your comments.

EPA Reg#/ File Symbol: 73049-460 CSF(s) dated: 3/22/11 REVIEW DUE DATE: 7/12/11

1. Compare CSF with prior CSF(s), and determine what is different.
Notes: Manufacturing Process changes altered impurity percentages.

2. Examine label. Does this product have food or feed use sites? Yes.

3. Is each field filled out on CSF? ☑yes ☐ no
Missing: NA

4. Is box 18 signed? ☑yes ☐no

5. Are addresses complete, including zipcodes in boxes 1, 2, and 11? ☑yes ☐no
Deficiencies:

6. Have they enclosed a Material Safety Data Sheet (MSDS) for each new ingredient?
☑yes ☐no
Deficiencies: NA.

7. In column 10. for each component is the chemical name, trade name and CAS No. listed? Is it clear what each component is? For any microbial ingredient, in column 10 - the description should include Colony forming units per gram (CFU/g) and cell collection identity number (E.g. ATCC 889-34.) ☑yes ☐no
Deficiencies: NA. Everything is accounted for.

8. Using a chemical catalog, or Refs verify the CAS #, and chemical name for each component under consideration. Also Note any toxicological information disclosed in catalog.
Deficiencies: NA. CAS#s are correct.

9. Determine PC codes for each component and write these in "EPA USE ONLY" column. Does each component have a PC Code? If code(s) are not found, it may be necessary to send request form to RD. ☑yes ☐no

10. For each inert component determine whether it is listed under 40 CFR 180.1001 (910-960). And write these codes in "EPA USE ONLY" column. (Names may be confusing- consult with a chemist if needed) *If this product is for feed or food use, all inert ingredients **MUST** have appropriate clearance.*
Deficiencies: No inerts. Impurities all clear.

11. For each inert component that does not have 40 CFR clearance determine whether it is a list 1, 2, 3, 4(a) , or 4(b) inert. Write this information in"EPA USE ONLY" column. References to consult: www.epa.gov/opprd001/inerts and FR Vol. 63, No. 121 pages 34384-34390. If any of the inert ingredients are listed as "No longer used" in the above FR vol.63 notice, or are on list 1 or 2, this is a problem to bring attention to chemist.
Problem inerts? NA. Impurities Clear.

12. If product used on food or feed, confirm active ingredient(s) has an established tolerance or exemption from food tolerance. (Consult Alphabetical listing in part 180 of 40 CFR pages 296-300, or the pesticide petition file jacket) ☐ yes ☑ no
Deficiencies: 180.1281.

13. Do certified limits for EACH component agree with 40 CFR 158.175?

Amount in Column 13 b.	Prescribed limits	Upper Limit	Lower Limit
≤1%	N ± 10%N	N x 1.1	N x 0.9
>1% but ≤20%	N ± 5%N	N x 1.05	N x 0.95
>20%	N ± 3%N	N x 1.03	N x 0.97

N= amount in Column 13 b. = nominal concentration

Calculate upper and lower limits using table above and compare with those listed in columns 14 a. and 14 b. of submitted CSF. If they do not agree, identify difference(s): Proposed limits of nominal active accepted.

14. Does the sum of the numbers in column 13. a. equal total listed in box 17?
☑ yes ☐no

15 Does column 13. b. add up to 100%? ☑ yes ☐no

16. If Alternative Formulation box is checked in box A- Is there another CSF for a Basic Formulation on file?? ☐yes ☐no ☑NA

17. Other issues? No.

Label Review

File Symbol: 73049-460) **Date:** 7/20/11 **Reviewer:** Chris Pfeifer

Site/Use	[Res /Ag /Both] [Food /Non-Food /Both]				
Tox Categories: (W)aived	[AcOral: 4 /AcDerm: 4 /AcInhl: 4 /EyeIrr: 3 /SkinIrr: 4 DermSens: N]				
Label Requirement	**Acceptable**	**Not Acceptable**	**N/A**	**Comments Recommendations**	**LRM3**
Restricted Use Pesticide	---	---	---		**Ch 6**
Product Name	✓				Pg 12-3
Compny Name and Info	✓				Pg 15-1
Identification Numbers	✓				**Ch 14**
Net Contents	✓				**Ch 17**
Ingredients Statement	✓			Percentage changed.	**Ch 5**
Label Claims	✓				**Ch 12**
Alternate Formula			✓		5-12

Precautionary Statements					
Label Requirement	**Acceptable**	**Not Acceptable**	**N/A**	**Comments Recommendations**	**LRM3**
KOROC	✓				3-1 & 9 7-3 & 4
Signal Word	✓				**Ch 3 Ch 7** **Ch 10**
General Heading Precautionary Statements	✓				Ch 7
First Aid (PRN 20001-1)	✓				**Ch 3 & 7**
Hazards to Humans and Domestic Animals	✓				**Ch 3, 7-3**
PPE (WPS) Engineering Controls	✓				Ch 7,Pg 7-12 Pgs 10-4, 15
User Safety Requirements	✓				Ch 10
User Safety Recommendations	✓				Ch 10
Environmental Hazards	✓				Ch 8
Physical and Chemical Hazards			✓		Pg 3-4 **Ch 9**

Directions for USE (FIFRA Text, WPS plus Storage and Disposal)					
Label Requirement	**Acceptable**	**Not Acceptable**	**N/A**	**Comments Recommendations**	**LRM3**
Header Directions for Use	✓				10-16
Violation of Federal Law text	✓				10-26, **11-7**
WPS Text (PPE)	✓				Ch 10, 7-1 7-11
Non-WPS Text	✓				7-12, **Ch 10**
Storage and Disposal	✓				11-16, **Ch 13**

Directions for Use (General Instructions and Information)					
Label Requirement	**Acceptable**	**Not Acceptable**	**N/A**	**Comments Recommendations**	**LRM3**
General Instructions and Sub-Header	✓				
Chemigation / Prohibition	✓				PRN
REI	✓				Pg 10-20

Label Requirement	**Acceptable**	**Not Acceptable**	**N/A**	**Comments Recommendations**	**LRM3**
General Info. (non-site specific info. on uses, pests, mixing, and loading, tank mixing, etc.)	✓				
General Precautions and Restrictions	✓				
Directions for Use					
Directions for Application	✓				
Warranty Information					
Consistency with label instructions	✓				12-6
Not false or misleading	✓				

"The warranty section contains an overly broad statement concerning limitations of liability. As such, this statement may be misleading and may constitute misbranding under the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA). It is suggested that the existing statement be preceded by the phrase, **To the extent allowable by state law**, or otherwise qualified to make it clear that this warranty is not intended to be a statement of law which implies that the buyer has no legal rights to recover damages from the manufacturer if he/she suffered a loss or injury from the product and concludes that it would be futile to pursue what might in reality be a valid claim."

S-Abscisic Acid
PC Code: 272000

DP Number(s): 388672
EPA Reg. or File Symbol Nos.73049-460

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

JUN 2 3 2011

Date: June 23, 2011

OFFICE OF CHEMICAL SAFETY AND POLUTION PREVENTION/OFFICE OF PESTICIDE PROGRAMS

MEMORANDUM

SUBJECT: Science Review of updated manufacturing process for technical registered product VBC 30054, containing 97.7 % w/w enantiomer S-Abscisic acid, Technical Grade Active Ingredient (TGAI), and adjusted composition of derived end use products, Pro Tone SG (EPA Reg. No. 73049-461) and Con Tego Pro SL (EPA Reg. No. 73049-462).

Decision Number: 446993
DP Number: 355133
EPA File Symbol Number: 73049-460
Chemical Class: Biochemical
PC Code: 272000
CAS Number: 21293-29-8
Active Ingredient Tolerance Exemptions:
MRID Numbers: 484305-01; -02, and – 03.

FROM: Clara Fuentes, Ph.D. Entomologist
Biochemical Pesticides Branch
Biopesticides & Pollution Prevention Division (7511P)

TO: Chris Pfeifer, Regulatory Action Leader
Biochemical Pesticides Branch
Biopesticides & Pollution Prevention Division (7511P)

ACTION REQUESTED

Valent biosciences Corporation has updated five batch analysis, certification of limits and manufacturing process for technical (TGAI) registered product VBC 30054, and adjusted the composition of its derived end use products, Pro Tone SG (EPA Reg. No. 73049-461) and Con Tego Pro SL (EPA Reg. No. 73049-462). In support of this action, the registrant has submitted

MRIDs 484305-01, 484305-02 and 484305-03; copies of upgraded CSFs for TGAI, and adjusted end use formulations, and 5 copies of upgraded product labels of TGAI (S-ABA, VBC-30054).

RECOMMENDATIONS AND CONCLUSIONS

Product Chemistry: Acceptable.

STUDIES SUMMARY

Refer to Confidential Appendix for summary of study reports MRIDs 484305-01; 484305-02, and 484305– 03.

cc: Reviewer: Clara Fuentes; RAL: Chris Pfeifer, BPPD Chron File, IHAD/ARS
FT, PY-S: date: 6/23 /11

Confidential Appendix

STUDIES SUMMARY

TABLE 1. Nominal CSF concentrations and certified limits for S-ABA, VBC-30054					
Ingredients (CAS number)	**PC Code**	**Purpose**	**Concentration (% by weight)**		
			Nominal	**Upper**	**Lower**
Active Ingredient					
S-Abscisic acid (S-ABA) (21293-29-8)	272000	Active ingredient	97.7	100.6	94.8
[redacted]					

Manufacturing process information may be entitled to confidential treatment

TABLE 2. Nominal CSF concentrations and certified limits for ConTego Pro SL

Ingredients (CAS number)	PC Code	Purpose	Concentration (% by weight)		
			% by Weight	Upper	Lower
Active Ingredient					
S-Abscisic acid (S-ABA) (97.7%) (21293-29-8)	272000	Active ingredient	10.24 (10.00)	10.75 (10.50)	9.73 (9.50)
[redacted]					

Inert ingredient information may be entitled to confidential treatment

Inert ingredient information may be entitled to confidential treatment

Manufacturing process information may be entitled to confidential treatment

S-Abscisic Acid
PC Code: 272000

DP Number(s): 388672
EPA Reg. or File Symbol Nos.73049-460

TABLE 3. Nominal CSF concentrations and certified limits for ProTone SG

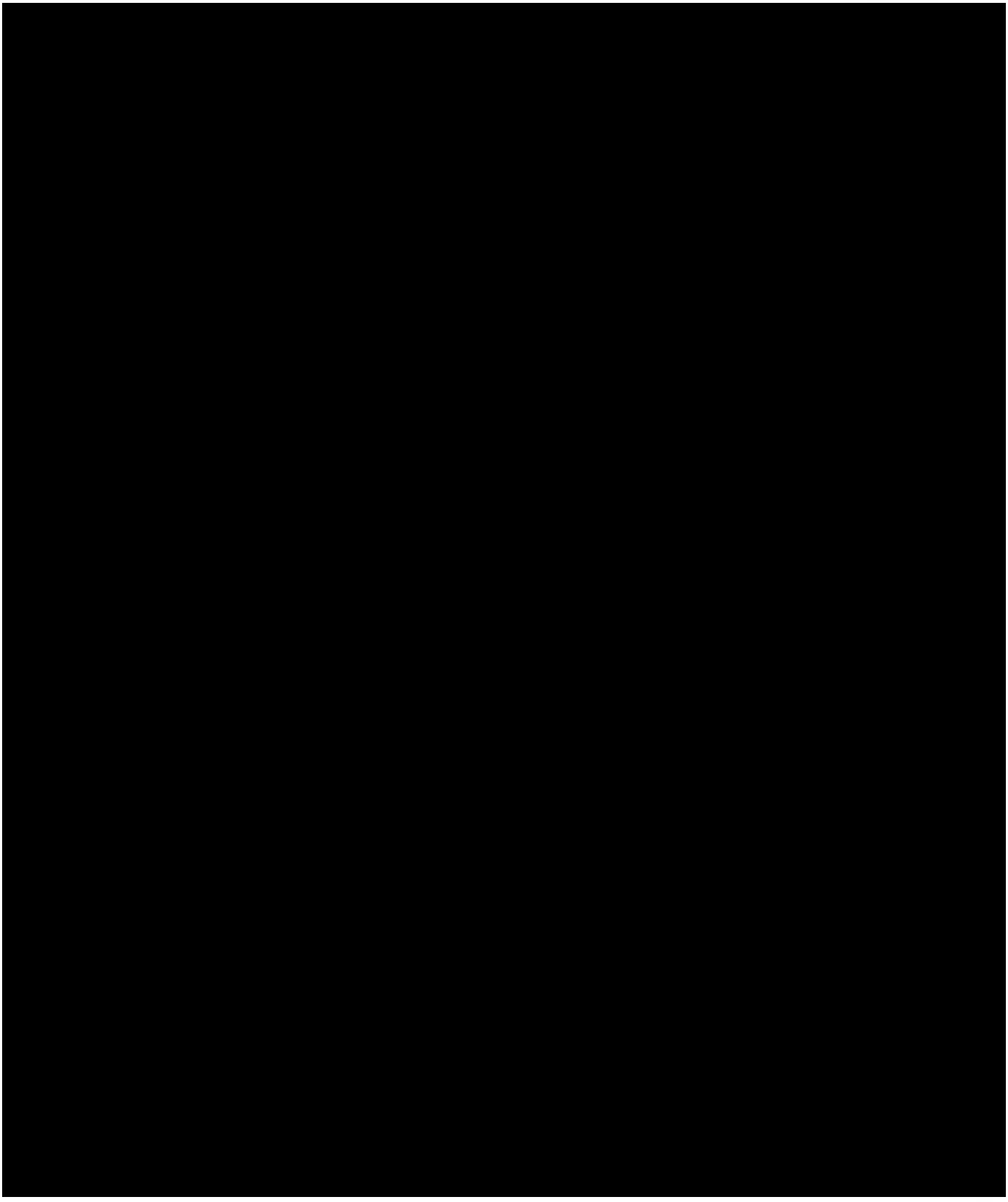
Ingredients (CAS number)	PC Code	Purpose	Concentration (% by weight)		
			% by Weight	Upper	Lower
Active Ingredient					
S-Abscisic acid (S-ABA) (97.7%) (21293-29-8)	272000	Active ingredient	20.47 (20.00)	21.49 (21.00)	19.45 (19.00)

[redacted]

Manufacturing process information may be entitled to confidential treatment

S-Abscisic Acid
PC Code: 272000

DP Number(s): 388672
EPA Reg. or File Symbol Nos.73049-460



Manufacturing process information may be entitled to confidential treatment

S-Abscisic Acid
PC Code: 272000

DP Number(s): 388672
EPA Reg. or File Symbol Nos.**73049-460**

[redacted]

MRID 484305-02: Preliminary Analysis and Certification of Product Ingredients.

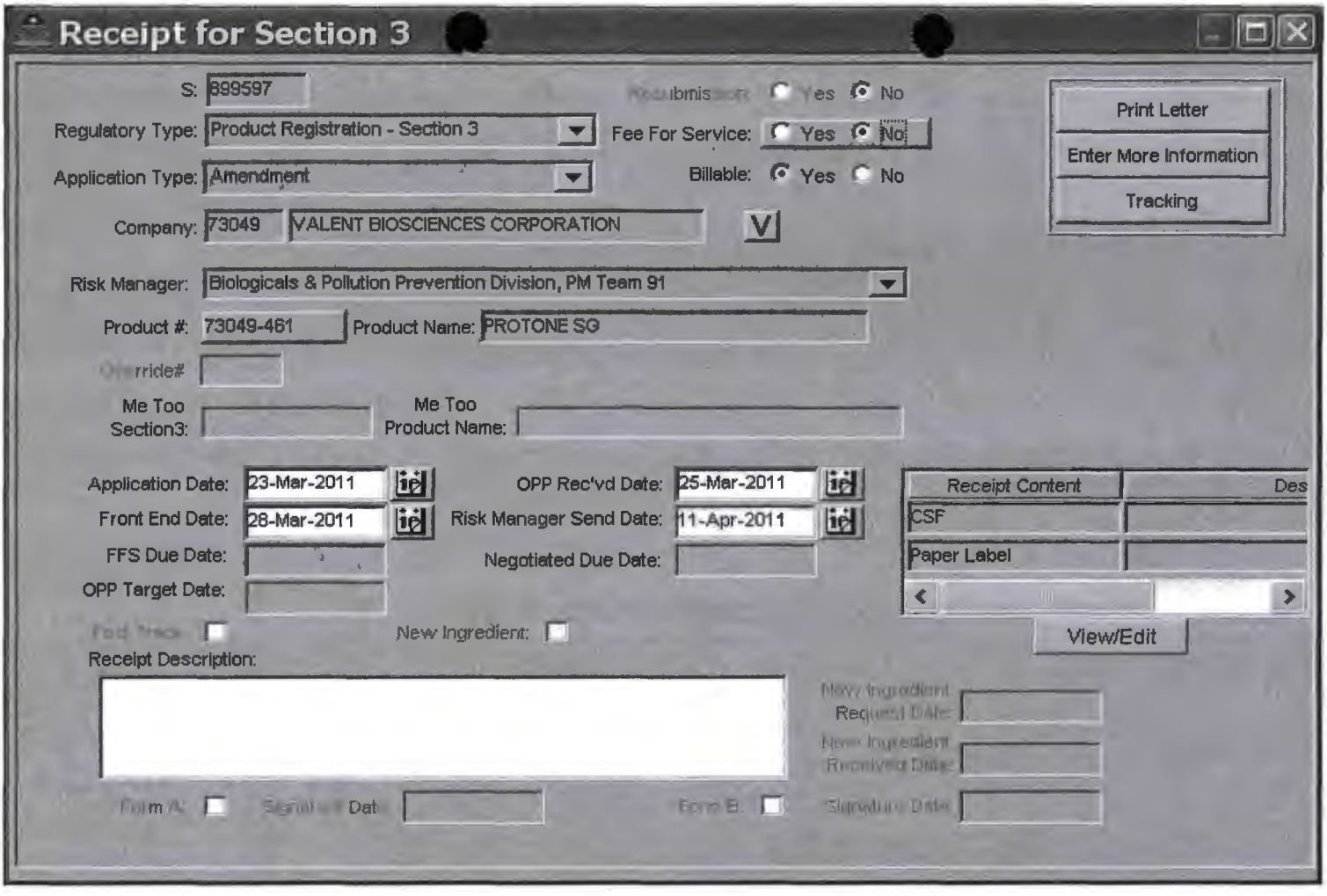
[redacted]

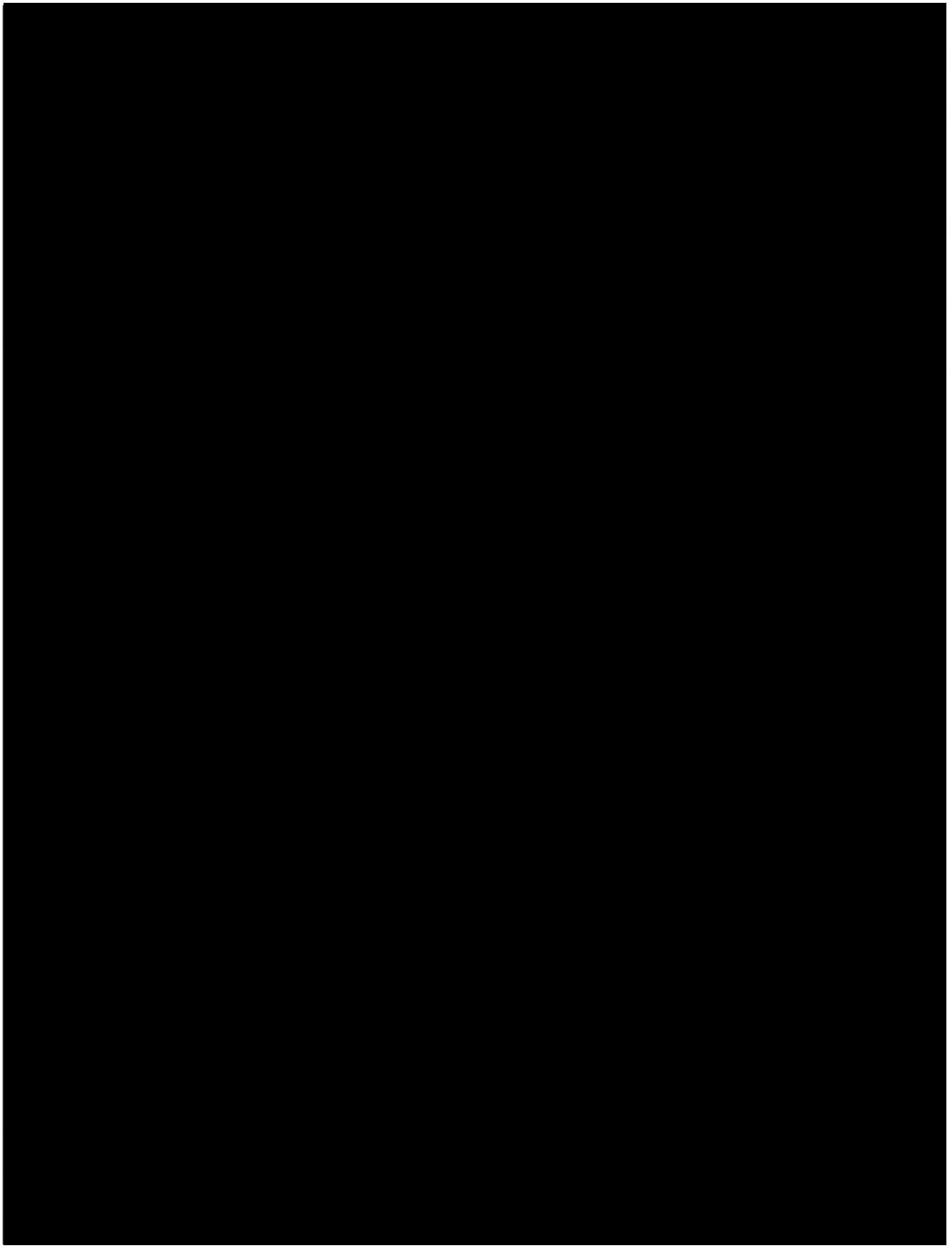
Manufacturing process information may be entitled to confidential treatment

S-Abscisic Acid
PC Code: 272000

DP Number(s): 388672
EPA Reg. or File Symbol Nos.73049-460

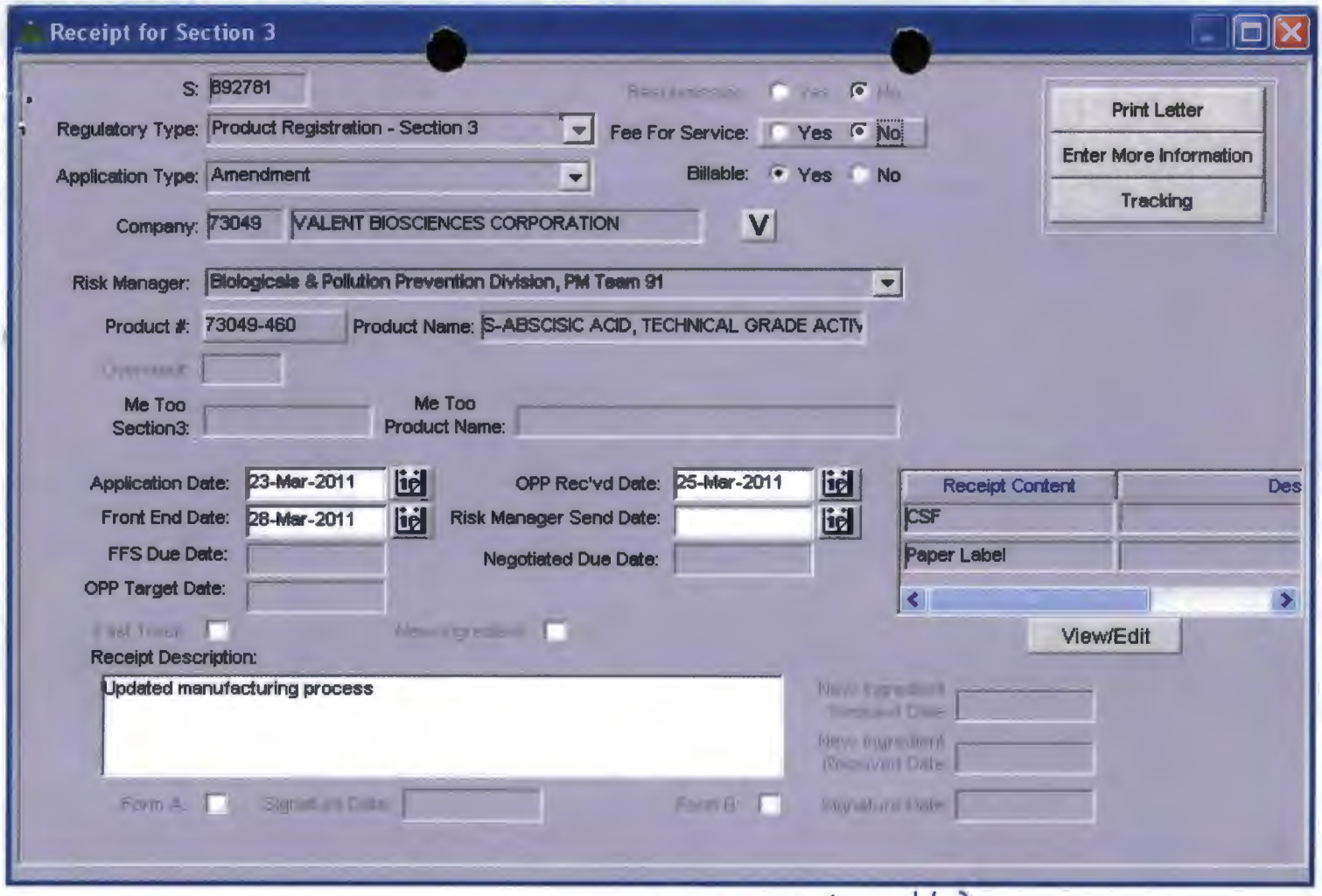
MRID 484305-03: Certification of Limits.


Receipt for Section 3
S: 899597
Resubmission: Yes No
Regulatory Type: Product Registration - Section 3
Fee For Service: Yes No
Application Type: Amendment
Billable: Yes No
Company: 73049 VALENT BIOSCIENCES CORPORATION
Print Letter
Enter More Information
Tracking
Risk Manager: Biologicals & Pollution Prevention Division, PM Team 91
Product #: 73049-461
Product Name: PROTONE SG
Override#
Me Too Section3:
Me Too Product Name:
Application Date: 23-Mar-2011
OPP Rec'vd Date: 25-Mar-2011
Front End Date: 28-Mar-2011
Risk Manager Send Date: 11-Apr-2011
FFS Due Date:
Negotiated Due Date:
OPP Target Date:
Receipt Content
Des
CSF
Paper Label
Fast Track:
New Ingredient:
View/Edit
Receipt Description:
New Ingredient Request Date:
New Ingredient Received Date:
Form A:
Signature Dat
Form B:
Signature Date



Manufacturing process information may be entitled to confidential treatment

Pages 42-63 Inert ingredient/product ingredient source information may be entitled to confidential treatment



Decis# 446993

B680 (4 months)

FFS start: 4/15/11

PRIA due: 8/15/11

Phase 1: 5/15/11

No phase 2 or 3

Phase 4: ~~7/30/11~~ 6/30/11

Phase 5: ~~8/15/11~~ 8/15/11

PRIA 2 – 21 Day Content Screen Review Worksheet

(EPA/OPP Use Only)

3/23/09

21 Day Screen Start Date: 3-25-11

Experts In-Processing Signature: MF Harrington Date 3-28-11 Fee Paid: Yes ✓

Division management contacted on issues No_____Yes _____Date _____

EPA Reg. Number: 73049-460	EPA Receipt Date: 3-25-11

	Items for Review	Yes	No	N/A*
1	**Application Form** (EPA Form 8570-1)(link to form) signed & complete including package type	X		
2	**Confidential Statement of Formula** all boxes completed, form signed, and dated (EPA Form 8570-4) (Link to form)	X		
	a) All inerts (link to http://www.epa.gov/opprd001/inerts/), including fragrances, approved for the proposed uses (see Footnote A) — yes: X; no:			
3	**Certification with Respect to Citation of Data** (EPA Form 8570-34) (Link to form) completed and signed (N/A if 100% repack)	X		
	Certificate and data matrix consistent	X		
	If applicant is relying on data that are compensable, is the offer to pay statement included. (see Footnote B) — yes: ; no:			
	If applicable, is there a letter of Authorization for exclusive use only.			
4	**Formulator's Exemption Statement** (EPA Form 8570-27) (Link to form) completed and signed (N/A if source is unregistered or applicant owns the technical)			X
5	**Data Matrix** (EPA Form 8570-35) (Link to form) both internal and external copies (PR 98-5) (Link to PR 98-5) completed and signed (N/A if 100% repack)	X		
	a) Selective Method (Fee category experts use) — yes: ; no:			
	b) Cite-All (Fee category experts use) — yes: X; no:			
	c) Applicant owns all data (Fee category experts use) — yes: ; no:			
6	**5 Copies of Label (link to http://www.epa.gov/oppfead1/labeling/lrm/) (Electronic labels on CD are encouraged and guidance is available)(link to** http://www.epa.gov/pesticides/regulating/registering/submissions/index.htm#labels)	X		

7	**Is the data package consistent with PR Notice 86-5** (link to PRN 86-5)	X		
8	**Notice of Filing (link to http://www.epa.gov/pesticides/regulating/tolerance_petitions.htm) included with petitions (link to http://www.epa.gov/pesticides/regulating/tolerances.htm)**			X
9	**If applicable for conventional applications, reduced risk rationale (link to http://www.epa.gov/opprd001/workplan/reducedrisk.html)**			X
10	**Required Data (link to http://www.epa.gov/pesticides/regulating/data_requirements.htm) and/or data waivers. See Footnote C.**			X
	a) List study (or studies) not included with application			

Comments:

REGISTRANT CONTACTED REGARDING FORM INCONSISTENCIES. REVISED FORM DELIVERED. 3/24/11 DP

COMPANY CONTACTED REGARDING CONFIDENTIALITY ISSUES WITH ONE OF THE SUBMITTED STUDIES. A REFORMATTED STUDY HAS BEEN SUBMITTED. 4/7/11

MRID 484305

* N/A – Not Applicable

Footnotes

A. During the 21 day initial content review, all CSFs will be reviewed to determine whether all inerts listed, including fragrances, are approved for the proposed uses. If an unapproved inert is identified, the applicant must either 1) resolve the inert issue by, for example, removing the inert, substituting it with an approved inert, submitting documentation that EPA approved the inert for the proposed pesticidal uses, correcting mistakes on the CSF, etc. or 2) provide the data to support OPP approval of the inert or 3) withdraw the application. Removing or substituting an inert ingredient will require a new CSF and may require submission of data. All information, forms, data and documentation resolving the inert issue must have been received by the Agency or the application withdrawn within the 21 day period, otherwise, the Agency will reject the application as described below.

To successfully complete this aspect of the 21 day initial content screen, applicants are **strongly encouraged** to verify that all inert ingredients have been approved for the application's uses **even if a product is currently registered** by consulting the inert Web

site [link to http://www.epa.gov/opprd001/inerts/lists.html] and if the inert is not approved, to **obtain the necessary inert approval prior to submitting an application to register a pesticide product containing that inert ingredient.** Some inert ingredients are no longer approved for food uses or certain types of uses. The name and/or CAS number on a CSF must match the name and CAS number on this web site. Simple typographical errors in the name or CAS number have resulted in processing delays.

If an inert is not listed on the inert ingredient web site and the applicant believes that the inert has been approved, the applicant should contact the Inert Ingredient Assessment Branch (IIAB) at inertsbranch@epa.gov and resolve the issue. Copies of the correspondence with IIAB resolving the issue should accompany the application. All new inerts except PIP inerts are reviewed by IIAB. The IIAB should also be contacted for any questions on what supporting data needs to be submitted for and the Agency's inert review process. Questions on PIP inerts should be directed to the Chief of Microbial Pesticides Branch [Link to http://www.epa.gov/oppbppd1/biopesticides/contacts_bppd.htm].

When a brand, trade, or proprietary name of an inert ingredient is listed on a CSF, additional information such as an alternate name of the inert, CAS number or other information [link to http://www.epa.gov/opprd001/inerts/tips.pdf] must also be included to enable the Agency to determine if it has been approved. Each component of an inert mixture (including a fragrance) must be identified. In some cases, the supplier of the mixture or fragrance may need to provide this information to the Agency. Prior to the Agency's receipt of an application, applicants must arrange with a proprietary mixture or fragrance supplier to provide the component information to the Agency or promptly upon EPA's request. If the inert ingredients in a proprietary blend (including fragrances) cannot or are not identified or provided within the 21-day content review period, the Agency will reject the application.

During the 21 day content review, applicants should submit information to the individual identified by the Agency when the applicant is informed of an unapproved inert.

Unapproved Inerts Identified on CSFs

All applications except conventional new products and PIPs

Once an unapproved inert is identified on a CSF, the Agency will contact the applicant with the following options:

1. Correct the application by, for instance, correcting the inert's identity or CAS number, providing documentation that the inert has been approved, or removing the unapproved inert from the CSF or replacing it with one that is approved for the application's uses; or

2. Submit the information and data needed for the Agency to approve the unapproved inert. If this option is selected and implemented, the Agency may request an extension in the PRIA decision review timeframe to accommodate the inert review/approval process;

3. Withdraw the application (the Agency retains 25% of the full fee for the fee category estimated); or

If none of these options is selected and implemented by the applicant within the 21 day content review period, the Agency will reject the application and retain 25% of the full fee of the category identified.

Conventional New Product Applications

When the Registration Division identifies an unapproved inert on a CSF with an application for a new product that the applicant has not identified as requiring an inert approval (R311, R312 or R313), it will contact the applicant with the following options:

1. Correct the application by, for instance, correcting the inert's identity or CAS number, providing documentation that the inert has been approved, or removing the unapproved inert from the CSF or replacing it with one that is approved for the application's uses; or

2. Submit the information and data needed for the Agency to approve the unapproved inert, including any required petition to establish or amend a tolerance or exemption from a tolerance. (This option may change the PRIA category for the application, which could require a longer decision review time and a larger fee. If additional fees are due, they must be received by the Agency within the 21 day content review period.)

3. Withdraw the application (the Agency retains 25% of the full fee for the fee category estimated); or

If none of the above options is selected and implemented during the 21-day content-review period, the Agency will reject the application and retain 25% of the appropriate fee for the new product-inert approval category.

PIP Applications

When the Biopesticide and Pollution Prevention Division identifies an unapproved inert on a PIP CSF and a request to approve the inert does not accompany the application, it will contact the applicant with the following options:

1. Correct the application by, for instance, correcting the spelling or name of the inert to that in 40 CFR 174, or providing documentation that the inert has been approved; or

2. Submit the information and data needed for the Agency to approve the unapproved inert. If an inert ingredient tolerance exemption petition is required, the petition must be received by the Agency and the B903 fee paid within the 21 day period. If this option is selected and implemented, the Agency will discuss harmonizing the timeframe for both actions.

3. Withdraw the application (the Agency retains 25% of the full fee for the fee category estimated); or

If none of the above options is selected and implemented during the 21 day content review period, the Agency will reject the application and retain 25% of the fee.

B. A policy on documentation of offers to pay is still being developed, however, for a me-too or fast track (similar/identical) new product, R300 or A530, an application without the necessary authorizations of offers to pay will be placed into either R301 or A531. The Agency recommends that authorizations of offers to pay be submitted with other PRIA applications to avoid delays in the Agency's decision.

C. Biopesticide applicants are advised to contact the Agency and discuss study waivers prior to submitting their application to the Agency. Documentation of such discussions should be submitted with the study waiver.

RE: Regarding Issues with Amendment 73049-460 (S-Abscisic Acid, TGAI)

Bade, Thomas to Anthony Ashe 03/29/2011 12:59 PM

History: This message has been replied to.

Attached is the corrected form. Thank you for the opportunity to easily fix this mistake. Please let me know if I can fix anything else, or answer any questions you might have.

-----Original Message-----
From: Ashe.Anthony@epamail.epa.gov [mailto:Ashe.Anthony@epamail.epa.gov]

Sent: Tuesday, March 29, 2011 9:13 AM
To: Bade, Thomas
Subject: Regarding Issues with Amendment 73049-460 (S-Abscisic Acid, TGAI)

Mr. Bade,

This message is being sent regarding an issue found during the initial screening of the above-mentioned amendment. On form 8570-34 (Certification with Respect to Citation of Data), the "cite-all" method of data support, which is in direct conflict with data listed as owned on the Data Matrix. These two forms must be consistent. The easiest fix is to resubmit form 8570-34, with "selective" chosen as the method of data support (please note that there is a cite-all option listed under this choice). The corrected form can be delivered to me via email, or fax (703-305-5060). If you have any questions, feel free to contact me. Additionally, the submitted studies are in the process of being reviewed. Should there be any issues to resolve with them, I will contact you. Thank you for your attention to this matter.

Sincerely,

Anthony H. Ashe
MacFadden Contractor
(703)305-0073

EPA Form 8570-34 Corrected signed.pdf

Bade, Thomas

From: paygovadmin@mail.doc.twai.gov
Sent: Wednesday, March 23, 2011 9:15 AM
To: Bade, Thomas
Subject: Pay.Gov Payment Confirmation

THIS IS AN AUTOMATED MESSAGE. PLEASE DO NOT REPLY.

Your transaction has been successfully completed.

Transaction Summary

Application Name: PRIA Service Fees
Pay.gov Tracking ID: 252TP5SE
Agency Tracking ID: 74186528656

Name On Account: Valent BioSciences Corporation Transaction Type: ACH Debit Transaction
Amount: $4,631.00 Payment Date: Mar 24, 2011 Account Type: Business Checking Routing
Number: [redacted]

Transaction Date: Mar 23, 2011 10:15:09 AM Number of Payments Scheduled: 1
Frequency: OneTime
Decision Number:
Registration Number:
Company Name: Valent BioSciences Corp
Company Number: 73049
Action Code: B680

Commercial/financial information may be entitled to confidential treatment

Please read instructions on reverse before completing form. Form Approved. OMB No. 2070-0060

Print Form

United States
Environmental Protection Agency
Washington, DC 20460

- [ ] Registration
- [ ] Amendment
- [x] Other

OPP Identifier Number

Application for Pesticide - Section I

1. Company/Product Number	2. EPA Product Manager	3. Proposed Classification
Valent BioSciences, EPA # 73049-460	Linda Hollis	[x] None [ ] Restricted
4. Company/Product (Name) Valent BioSciences / VBC-30054 (S-Abscisic Acid)	PM#	

5. Name and Address of Applicant *(Include ZIP Code)*

Valent BioSciences Corp.
870 Technology Way
Libertyville IL, 60048

[ ] *Check if this is a new address*

6. Expedited Review. In accordance with FIFRA Section 3(c)(3)(b)(i), my product is similar or identical in composition and labeling to:

EPA Reg. No. 73049-460

Product Name S-Abscisic Acid

Section - II

- [ ] Amendment - Explain below.
- [ ] Resubmission in response to Agency letter dated _____
- [ ] Notification - Explain below.
- [ ] Final printed labels in response to Agency letter dated _____
- [ ] "Me Too" Application.
- [ ] Other - Explain below.

Explanation: Use additional page(s) if necessary. (For section I and Section II.)

Updated five lot analysis and manufacturing directions.

Section - III

1. Material This Product Will Be Packaged In:

Child-Resistant Packaging	Unit Packaging	Water Soluble Packaging	2. Type of Container
[ ] Yes* [x] No	[ ] Yes [x] No	[ ] Yes [x] No	[ ] Metal [x] Plastic [ ] Glass [ ] Paper [ ] Other (Specify) _____
* *Certification must be submitted*	If "Yes" Unit Packaging wgt. / No. per container	If "Yes" Package wgt / No. per container	

3. Location of Net Contents Information	4. Size(s) Retail Container	5. Location of Label Directions
[x] Label [ ] Container		[ ] On Label [x] On Labeling accompanying product

6. Manner in Which Label is Affixed to Product [x] Lithograph / Paper glued / Stenciled [ ] Other _____

Section - IV

1. Contact Point *(Complete items directly below for identification of individual to be contacted, if necessary, to process this application.)*

Name	Title	Telephone No. (Include Area Code)
Thomas Bade P.hD.	Regulatory Manager	847-968-4726

Certification

I certify that the statements I have made on this form and all attachments thereto are true, accurate and complete. I acknowledge that any knowingly false or misleading statement may be punishable by fine or imprisonment or both under applicable law.

6. Date Application Received (Stamped)

2. Signature	3. Title	4. Typed Name	5. Date
Thomas Bade	Regulatory Manager	Thomas Bade	3/22/11

EPA Form 8570-1 (Rev. 8-94) Previous editions are obsolete. White - EPA File Copy (original) Yellow - Applicant Copy

Form Approved OMB Nos. 2070-0060; 2070-0057; 2070-0107; 2070-0122; 2070-0164

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
1200 Pennsylvania Avenue, N.W.
WASHINGTON, D.C. 20460

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Certification with Respect to Citation of Data

Applicant's/Registrant's Name, Address, and Telephone Number Valent BioSciences, 870 Technology Way, Libertyville Illinois 60048	EPA Registration Number/File Symbol 73049-460
Active Ingredient(s) and/or representative test compound(s) S- Abscisic acid (EPA Registration # 73049-460)	Date October 25, 2010
General Use Pattern(s) (list all those claimed for this product using 40 CFR Part 158) Plant growth regulator - Technical Grade Active Ingredient	Product Name S-Abscisic acid (S-ABA)

NOTE: If your product is a 100% repackaging of another purchased EPA-registered product labeled for all the same uses on your label, you do not need to submit this form. You must submit the Formulator's Exemption Statement (EPA Form 8570-27).

☐ I am responding to a Data-Call-In Notice, and have included with this form a list of companies sent offers of compensation (the Data Matrix form should be used for this purpose).

SECTION I: METHOD OF DATA SUPPORT (Check one method only)

☐ I am using the cite-all method of support, and have included with this form a list of companies sent offers of compensation (the Data Matrix form should be used for this purpose).	☑ I am using the selective method of support (or cite-all option under the selective method), and have included with this form a completed list of data requirements (the Data Matrix form must be used).

SECTION II: GENERAL OFFER TO PAY

[Required if using the cite-all method or when using the cite-all option under the selective method to satisfy one or more data requirements]

☐ I hereby offer and agree to pay compensation, to other persons, with regard to the approval of this application, to the extent required by FIFRA.

SECTION III: CERTIFICATION

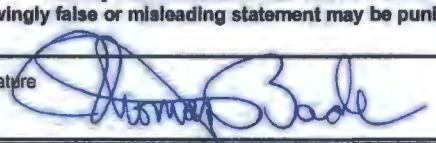
I certify that this application for registration, this form for reregistration, or this Data-Call-In response is supported by all data submitted or cited in the application for registration, the form for reregistration, or the Data-Call-In response. In addition, if the cite-all option or cite-all option under the selective method is indicated in Section I, this application is supported by all data in the Agency's files that (1) concern the properties or effects of this product or an identical or substantially similar product, or one or more of the ingredients in this product; and (2) is a type of data that would be required to be submitted under the data requirements in effect on the date of approval of this application if the application sought the initial registration of a product of identical or similar composition and uses .

I certify that for each exclusive use study cited in support of this registration or reregistration, that I am the original data submitter or that I have obtained the written permission of the original data submitter to cite that study.

I certify that for each study cited in support of this registration or reregistration that is not an exclusive use study, either: (a) I am the original data submitter; (b) I have obtained the permission of the original data submitter to use the study in support of this application; (c) all periods of eligibility for compensation have expired for the study; (d) the study is in the public literature; or (e) I have notified in writing the company that submitted the study and have offered (i) to pay compensation to the extent required by sections 3(c)(1)(F) and/or 3(c)(2)(B) of FIFRA; and (ii) to commence negotiations to determine the amount and terms of compensation, if any, to be paid for the use of the study.

I certify that in all instances where an offer of compensation is required, copies of all offers to pay compensation and evidence of their delivery in accordance with sections 3(c)(1)(F) and/or 3(c)(2)(B) of FIFRA are available and will be submitted to the Agency upon request. Should I fail to produce such evidence to the Agency upon request, I understand that the Agency may initiate action to deny, cancel or suspend the registration of my product in conformity with FIFRA.

I certify that the statements I have made on this form and all attachments to it are true, accurate, and complete. I acknowledge that any knowingly false or misleading statement may be punishable by fine or imprisonment or both under applicable law.

Signature	Date	Typed or Printed Name and Title
	3/29/11	Thomas Bade, Regulatory Manager

EPA Form 8570-34 (12-2003) Electronic and Paper versions available. Submit only Paper version.

Form Approved OMB No. 2070-0060

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
401 M Street, S.W.
WASHINGTON, D.C. 20460

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DATA MATRIX

Date	EPA Reg No./File Symbol 73049-460	Page 1 of 5
Applicant's/Registrant's Name & Address Valent BioSciences Corporation, 870 Technology Way, Livertyville, IL, 60048	Product VBC-30054 (S-Abscisic Acid); TGAI for Manufacturing Use Only	

Ingredient S-Abscisic Acid (S-ABA); (S)-5-(1-hydroxy-2,6,6-trimethyl-4-oxo-2-cyclohexen-1-yl)-3-methyl-(2Z,4E)-pentadienoic acid, [CAS # 21293-29-8]

Guideline Reference Number	Guideline Study Name	MRID Number	Submitter	Status	Note
880.1100, 880.1200, 880.1400	Integrated Manufacturing Process S-ABA # 30054; 056-4	46895601	Valent BioSciences EPA # 73049	OWN	
880.1100, 880.1200, 880.1400	Integrated Manufacturing Process S-ABA # 30054; 027-1	47067903	Valent BioSciences EPA # 73049	OWN	
830.1700, 830.1750, 830.1800	Product Chemistry: Analysis, Cert limits, # 30054; 056-5	46895602	Valent BioSciences EPA # 73049	OWN	
830.1700, 830.1750, 830.1800	Product Chemistry; Analysis, Cert limits, # 30054; 027-2	47067904	Valent BioSciences EPA # 73049	OWN	
830.1700	Technical 5-Lot Analysis, PTRL # 1473W	47470401	Valent BioSciences EPA # 73049	OWN	
830.1700	VBC-30054 Product Chem: Cert Limits # 30054; 127-2	47470403	Valent BioSciences EPA # 73049	OWN	
830.1800	Anal Mtd; Validation TGAI and formulation, PTRL# 1442W	46895610	Valent BioSciences EPA # 73049	OWN	
830.1700	Charaterization of 1-4 diol # VBCL07-48060-01	47470520	Valent BioSciences EPA # 73049	OWN	
830.0000	30054 Phys Chem Summary, # 30054; 056-3	46895603	Valent BioSciences EPA # 73049	OWN	
830.6302, 830.6303, 830.6304	30054 Phys Cehm Characteristics PRTL # 1438W	46895604	Valent BioSciences EPA # 73049	OWN	
830.6313	30054 Stability, Temp, Metals & Ions PTRL # 1618W-1	47470406	Valent BioSciences EPA # 73049	OWN	
830.6315	30054 Flamability, Explodability, HLS # ZAB0083/072858	47470410	Valent BioSciences EPA # 73049	OWN	
830.7000, 830.7300	30054 pH, PTRL # 1558W	46895607	Valent BioSciences EPA # 73049	OWN	
830.7200, 830.7300	30054 Melting Point, Density PTRL # 1438W	46895604	Valent BioSciences EPA # 73049	OWN	
830.7840, .7550, .7560, .7570	30054 water Sol, Part Coef, Diss Const, PTRL#1437W	46895605	Valent BioSciences EPA # 73049	OWN	

Signature	Name and Title	Date
Thomas Bade	Thomas Bade, Regulatory Manager	3/22/11

EPA Form 8570-35 (9-97) Electronic and Paper versions available. Submit only Paper version.

Agency Internal Use Copy

Form Approved OMB No. 2070-0060

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
401 M Street, S.W.
WASHINGTON, D.C. 20460

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DATA MATRIX

Date	EPA Reg No./File Symbol 73049-46C	Page 2 of 5
Applicant's/Registrant's Name & Address Valent BioSciences Corporation, 870 Technology Way, Livertyville, IL, 60048	Product VBC-30054 (S-Abscisic Acid); TGAI for Manufacturing Use Only	

Ingredient S-Abscisic Acid (S-ABA); (S)-5-(1-hydroxy-2,6,6-trimethyl-4-oxo-2-cyclohexen-1-yl)-3-methyl-(2Z,4E)-pentadienoic acid, [CAS # 21293-29-8]

Guideline Reference Number	Guideline Study Name	MRID Number	Submitter	Status	Note
830.0000	Lomon Phys Chem Summary # 2004B-04	47470413	Valent BioSciences EPA # 73049	OWN	
830.1800	Analytical HPLC Method # VBC-M04001.2		Valent BioSciences EPA # 73049	OWN	
830.7050	30054 - UV/Vis Abs, Spectra DeCode REP-RC-2004-048	47470414	Valent BioSciences EPA # 73049	OWN	
830.7050	30054 - Ref Std retest DeCode REP-RC-2005-039	47470415	Valent BioSciences EPA # 73049	OWN	
830.7950	30054 - Vapour Pressure, PTRL # 1436W-1	46895606	Valent BioSciences EPA # 73049	OWN	
830.7840	30054 - Solubility in Organic Solvents, PTRL # 1730W-1	47470411	Valent BioSciences EPA # 73049	OWN	
830.2110	30054 - Hydrolysis at pH 4, 7, 9, PTRL # 1729W-1	47470412	Valent BioSciences EPA # 73049	OWN	
880.1100, .1200, .1400	Integrated Manufacturing Process S-ABA 30054; 810-01		Valent BioSciences EPA # 73049	OWN	
830.1700, 830.1750	Analysis and Certification of Product Ingredients in 8-lots		Valent BioSciences EPA # 73049	OWN	
830.1750	S-ABA Product Chem: Certification of Limits		Valent BioSciences EPA # 73049	OWN	

Signature Thomas Bade

Name and Title Thomas Bade, Regulatory Manager

Date 3/22/11

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DATA MATRIX

Date	EPA Reg No./File Symbol 73049-460	Page 3 of 5
Applicant's/Registrant's Name & Address Valent BioSciences Corporation, 870 Technology Way, Livertyville, IL, 60048	Product VBC-30054 (S-Abscisic Acid); TGAI for Manufacturing Use Only	

Ingredient S-Abscisic Acid (S-ABA); (S)-5-(1-hydroxy-2,6,6-trimethyl-4-oxo-2-cyclohexen-1-yl)-3-methyl-(2Z,4E)-pentadienoic acid, [CAS # 21293-29-8]

Guideline Reference Number	Guideline Study Name	MRID Number	Submitter	Status	Note
870.1100	30054 - Acute Oral, PSL # 16974	46895611	Valent BioSciences EPA # 73049	OWN	
870.1200	30054 - Acute Dermal, PSL # 16975	46895612	Valent BioSciences EPA # 73049	OWN	
870.1300	30054 - Acute Inhalation, PSL # 17515	46895613	Valent BioSciences EPA # 73049	OWN	
870.2400	30054 - Primary Eye Irriation, PSL # 16976	46895614	Valent BioSciences EPA # 73049	OWN	
870.2500	30054 - Primary Dermal Irritation, PSL # 16977	46895615	Valent BioSciences EPA # 73049	OWN	
870.2600	30054 - Dermal Sensitization, PSL # 16978	46895616	Valent BioSciences EPA # 73049	OWN	

Signature Thomas Bade

Name and Title Thomas Bade, Regulatory Manager

Date 3/22/11

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DATA MATRIX

Date	EPA Reg No./File Symbol 73049-460	Page 4 of 5
Applicant's/Registrant's Name & Address Valent BioSciences Corporation, 870 Technology Way, Livertyville, IL, 60048	Product VBC-30054 (S-Abscisic Acid); TGAI for Manufacturing Use Only	

Ingredient S-Abscisic Acid (S-ABA); (S)-5-(1-hydroxy-2,6,6-trimethyl-4-oxo-2-cyclohexen-1-yl)-3-methyl-(2Z,4E)-pentadienoic acid, [CAS # 21293-29-8]

Guideline Reference Number	Guideline Study Name	MRID Number	Submitter	Status	Note
870.3100	90-Day Oral Toxicity, CRL # 28084	47470510	Valent BioSciences EPA # 73049	OWN	
870.3250	21-Day Repeat Dermal, CRL # 27971	47470508	Valent BioSciences EPA # 73049	OWN	
870.3700	Teratology. preliminary Prenatal Dev, CRL # 28566	47470511	Valent BioSciences EPA # 73049	OWN	
870.3700	Teratology, Prenatal Development, # WIL-505004	47470512	Valent BioSciences EPA # 73049	OWN	
870.5100	Bacterial Reverse Mutation, Covance # 7194-101	47030901	Valent BioSciences EPA # 73049	OWN	
870.5300	In vitro cell gene mutation, Covance # 7194-103	47005301	Valent BioSciences EPA # 73049	OWN	
870.5375	In vitro cell gene mutation, Covance # 7194-102	47005302	Valent BioSciences EPA # 73049	OWN	
870.3050	4-week Oral Toxicity, CRL # 27720	47470509	Valent BioSciences EPA # 73049	OWN	
870.3100	13-Week Oral Toxicity, CRL # 28084	47470510	Valent BioSciences EPA # 73049	OWN	
N/A	Endocrine Disruptor Testing, #VBC-SCC ABA 12-14-07	47470513	Valent BioSciences EPA # 73049	OWN	

Signature Thomas Bade

Name and Title
Thomas Bade, Regulatory Manager

Date 3/22/11

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DATA MATRIX

Date	EPA Reg No./File Symbol 73049-460	Page 5 of 5
Applicant's/Registrant's Name & Address Valent BioSciences Corporation, 870 Technology Way, Livertyville, IL, 60048	Product VBC-30054 (S-Abscisic Acid); TGAI for Manufacturing Use Only	

Ingredient S-Abscisic Acid (S-ABA); (S)-5-(1-hydroxy-2,6,6-trimethyl-4-oxo-2-cyclohexen-1-yl)-3-methyl-(2Z,4E)-pentadienoic acid, [CAS # 21293-29-8]

Guideline Reference Number	Guideline Study Name	MRID Number	Submitter	Status	Note
850.2100	Acute Avian - 30054, WI # 529-111	47067901	Valent BioSciences EPA # 73049	OWN	
850.2200	Avian Dietary tox. Waiver S-ABA 30054: 058-1	47470521	Valent BioSciences EPA # 73049	OWN	
850.1075	Acute Fish - 30054, WI # 529A-104	47131402	Valent BioSciences EPA # 73049	OWN	
850.1010	Acute invertebrate, fresh water - 30054, WI # 529A-103	47131401	Valent BioSciences EPA # 73049	OWN	
850.4100, 850.4150	Non-target plant toxicity, S-ABA 30054;047-02	47131404	Valent BioSciences EPA # 73049	OWN	
850.4100, 850.4150	Non-target plant toxicity, S-ABA 30054;047-02REF	47153201	Valent BioSciences EPA # 73049	OWN	
850.4350	Non-target Insect-honeybee, EuGAB#20071029/S1BLEU	47151201	Valent BioSciences EPA # 73049	OWN	
N/A	EarthWorm Toxicity. WI # 529-119	47470514	Valent BioSciences EPA # 73049	OWN	
850.0000	Lomon Summary of EcoTox Results, # June 2000	47470515	Valent BioSciences EPA # 73049	OWN	
850.0000	Background Review of Literature, # ABA-LS2	47470518	Valent BioSciences EPA # 73049	OWN	
850.0000	Copies of background literture papers, # ABA-LS2 REF	47470519	Valent BioSciences EPA # 73049	OWN	
860.1500	Residue Analytical method, # S-ABA 30054; 106-1	46985604	Valent BioSciences EPA # 73049	OWN	
850.1500	Fate in Grapes, resdiue Levels, # S-ABA 30025; 086-1	47005303	Valent BioSciences EPA # 73049	OWN	
860.1360	Multiresidue method testing Waiver, S-ABA 30054; 058-2	47470522	Valent BioSciences EPA # 73049	OWN	

Signature Thomas Bade

Name and Title Thomas Bade, Regulatory Manager

Date 3/22/11

EPA Form 8570-35 (9-97) Electronic and Paper versions available. Submit only Paper version.

Agency Internal Use Copy

Transmittal Document

S-Abscisic Acid (S-ABA)
Technical grade Active Ingredient
EPA Registration # 73049-460

Submitter: Valent BioSciences Corp.
879 Technology Way
Libertyville, IL 60048

Regulatory Action: In support of the registration of the Technical Grade Active Ingredient (TGAI) S-Abscisic Acid, Reg # 73049-460.

Transmittal Date: March 22, 2011

Listing of Submitted Studies:

Document 1

Title: Integrated Manufacturing Process (VBC-30054 (S-Abscisic Acid)
Data requirements: OPPTS 880.1100, 880.1200, 880.1400
Study Date: November 3, 2010
Performing Laboratory: Valent BioSciences Corp. Research Center
870 Technology Way
Libertyville, IL 60048

Project ID: S-ABA 30054; 810-01

MRID No.: _____

Document 2

Title: Analysis and Certification of Product Ingredients in Selected Lots of S-Abscisic Acid
Data requirements: OPPTS 830.1700, 830.1750
Study Date: February 24, 2011
Performing Laboratory: Valent BioSciences Corp. Research Center.
6131 Oakwood Road
Long Grove, IL 60047

Project ID: VBCL10-48060-06

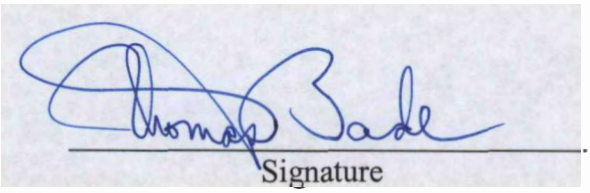
MRID No.: _____

Document 3

Title: S-Abscisic Acid: VBC-30054 TGAI Product Chemistry: Certification of Limits
Data requirements: OPPTS 830.1750
Study Date: March 22, 2011
Performing Laboratory: Valent BioSciences Corp.
870 Technology Way
Libertyville, IL 60048

Project ID: S-ABA 30054; 311-02

MRID No.: _____

Company Official: 
Signature

Company Name: Valent BioSciences Corporation

Company Contact: Thomas Bade Ph.D. 847-968-4726
Phone

VALENT BIOSCIENCES™
CORPORATION

870 TECHNOLOGY WAY
LIBERTYVILLE, IL 60048 - 800-323-9597

March 23, 2011

Document Processing Desk (REGFEE)
Office of Pesticide Programs (7504P)
U.S. Environmental Protection Agency
Room 266A, Crystal Mall 2
1921 Jefferson Davis Highway
Arlington, VA 22202

Attention: Mr. Chris Pfeifer
Regulatory Action Leader
Biopesticides and Pollution Prevention Division (7511P)
U.S. Environmental Protection Agency

Subject: Valent BioSciences Corp.
Updated Manufacturing Process for S-Abscisic Acid,
(EPA Reg.No.73049-460)

The following submission is an updated five-lot analysis, an updated certification of limits and an updated manufacturing process for the biochemical plant growth regulator S-Abscisic Acid (S-ABA, VBC-30054), EPA Reg.No.73049-460.

This is in continuation of many interactions and submissions presented to the United State Environmental Protection Agency (EPA), including the Section 3 registration of S-ABA TGAI (EPA Reg. No. 73049-460), and the registration of two end use formulations (ProTone SG; EPA Reg. No. 73049-461 and ConTego Pro SL; EPA Reg No. 73049-462).

Also, a tolerance exemption has been granted to S-Abscisic Acid; Federal Register: March 12, 2010 (Volume 75, Number 48)]; 40 CFR Part 180 [EPA-HQ-OPP-2009-0127; FRL-8814-5]

> "… exemption from the requirement of a tolerance for residues of the biochemical pesticide S-Abscisic Acid, (S)-5-(1-hydroxy-2,6,6-trimethyl-4-oxo-1-cyclohex-2-enyl)-3-methyl-penta-(2Z,4E)-dienoic Acid (ABA), to make it a permanent exemption from the requirement of a tolerance for residues of ABA in or on all food commodities when applied or used preharvest as a plant regulator."

S-Abscisic Acid is a naturally occurring plant growth regulator. It is naturally produced, utilized and metabolized by plants, in the course of natural plant physiology. It has been found at various concentrations in all plants in which it was looked for, and it's concentration in the environment is known to naturally fluctuate quite significantly depending upon plant growth stage and environmental conditions.

VALENT BIOSCIENCES CORPORATION

S-Abscisic Acid 'Technical Grade Active Ingredient (TGAI)' registered by Valent BioSciences is a natural product produced by a fermentation process. It is subsequently isolated and purified to give the Technical Grade Active Ingredient (TGAI) used in the Valent End Use products. This TGAI, being a fermentation product, is produced by an organism and therefore identical to S-ABA naturally produced by other organism in the environment.

Valent BioSciences believes this action fits the category of B680 "Label amendment requiring data submission" with a cost of $4,631 and a PRIA timeline of 4 months. The percent active ingredient listed on the label needs to be updated as a result of the new lot analysis study, (not significantly but a change does need to be made because the CSF has changed slightly). In addition, the CSFs for the two formulated product have to be changed to reflect the change in nominal % active in the active ingredient CSF.

Valent BioSciences has previously submitted payment for this registration action; [Pay.gov tracking ID: 252TP5SE, Name of account: Valent BioSciences Corp., Payment amount: $4,631.00, Payment date: March 24, 2011].

This EPA submission is organized as follows:

Cover letter
Administrative Documents
- Form 8570-1 EPA Pesticide Registration Application form
- Form 8570-34 Certification with Respect to Citation of Data
- Form 8570-35 Data Matrix (VBC-30054 [TGAI]),
- Form 8570-4 CSF (VBC-30054 [TGAI])
- Transmittal Document (listing all studies submitted)
- Copy of the Pay.gov tracking receipt, [Pay.gov tracking ID: 252TP5SE]
- Form 8570-4 CSF (ProTone SG, Reg #: 73049-461)
- Form 8570-4 CSF (ConTego Pro SL, Reg #: 73049-462)

One copy of the Label for TGAI: S-Abscisic Acid, Technical Grade Active Ingredient, (S-ABA, VBC-30054), with changes highlighted
Five copies of the Label for TGAI: S-Abscisic Acid, Technical Grade Active Ingredient, (S-ABA, VBC-30054)
Three copies of each study submitted

The reports contained within this submission pertain to description of the Manufacture of the TGAI, analysis of production lots of the TGAI and presentation of the certified limits. The new reports included in this submission are listed below;

VALENT BIOSCIENCES CORPORATION

Guideline	Data Requirement		VBC Report Number, issue date
880.1100	Product Identity		Report #: S-ABA 30054; 810-01, (Nov. 3, 2010)
880.1200	Description of Manufacturing		Report #: S-ABA 30054; 810-01, (Nov. 3, 2010)
880.1400	Discussion of Formation of Impurities		Report #: S-ABA 30054; 810-01, (Nov. 3, 2010)
830.1700	Preliminary Analysis		Report #: VBCL10-48060-06 (March 22, 2011)
830.1750	Certified Limits		Report #: S-ABA 30054; 311-02 (March 22, 2011)

Included in this application are; a transmittal document that lists three new studies submitted in support of this submission, three copies of each of these studies, five copies of the TGAI label, and on copy of the TGAI label with changes highlighted. Additionally, copies of revised CSFs (Form 8570-4) for the two end use products, (ProTone SG; EPA Reg. No. 73049-461 and ConTego Pro SL; EPA Reg No. 73049-462), containing changes resulting from the adjustment of the nominal concentration of the active in the TGAI, are included. These changes give a slight increase in the amount of TGAI added (because of the slight decrease in % ai in the TGAI), and concurrently a slight decrease in the amount of solvent of diluent added.

Please contact me at (847)-968-4726 (or at thomas.bade@valentbiosciences.com) if I can be of any assistance during the review of this application.

Sincerely,

Thomas Bade Ph.D.
Regulatory Manager
Valent BioSciences

DATA PACKAGE BEAN SHEET

Date: 14-Apr-2011

Decision #: 446993
DP #: (388672)
PRIA
Parent DP #:
Submission #: 892781

* * * Registration Information * * *

Registration: 73049-460 - S-ABSCISIC ACID, TECHNICAL GRADE ACTIVE INGREDIEN

Company: 73049 - VALENT BIOSCIENCES CORPORATION

Risk Manager: RM 91 - Andrew Bryceland - (703) 305-6928 Room# PY1 S-8911

Risk Manager Reviewer: Jay Pfeifer JPFEIFER

Sent Date: _____ Calculated Due Date: 15-Aug-2011 Edited Due Date: _____

Type of Registration: Product Registration - Section 3

Action Desc: (B680) AMENDMENT;NON-FAST TRACK;MICROBIAL/BIOCHEMICAL;

Ingredients: 272000, Abscisic acid(99.3%)

* * * Data Package Information * * *

Expedite: ○ Yes ● No Date Sent: 14-Apr-2011 Due Back: _____

DP Ingredient: 272000, Abscisic acid

DP Title: updated Manufacturing Process

CSF Included: ● Yes ○ No Label Included: ● Yes ○ No Parent DP #: _____

Assigned To		Date In	Date Out		
Organization:	BPPD / BPB	14-Apr-2011		Last Possible Science Due Date:	17-Apr-2011
Team Name:	RM 91	14-Apr-2011		Science Due Date:	
Reviewer Name:				Sub Data Package Due Date:	
Contractor Name:					

* * * Studies Sent for Review * * *

Printed on Page 2

* * * Additional Data Package for this Decision * * *

No Additional Data Packages

* * * Data Package Instructions * * *

Review for Acceptability

Phase 3-4 Due Date July 1

U.S. ENVIRONMENTAL PROTECTION AGENCY
Office of Pesticide Programs
Biopesticides and Pollution Prevention Division
(7511P)
1200 Pennsylvania Avenue NW
Washington, DC 20460

EPA Reg. Number:	Date of Issuance:
73049-460	28 February 2012
Term of Issuance:	Unconditional

NOTICE OF PESTICIDE:

__X__ Registration ____ Re-registration
(under FIFRA, as amended)

Name of Pesticide Product:

S-Abscisic Acid Technical Grade Active Ingredient

Name and Address of Registrant (include ZIP Code):
Valent BioSciences Corporation
870 Technology Way
Libertyville, IL 60048

Note: Changes in labeling differing in substance from that accepted in connection with this registration must be submitted to and accepted by the Biopesticides and Pollution Prevention Division prior to use of the label in commerce. In any correspondence on this product, always refer to the above EPA registration number.

On the basis of information furnished by the registrant, the above named pesticide is hereby registered/reregistered under the Federal Insecticide, Fungicide and Rodenticide Act.

Registration is in no way to be construed as an endorsement or recommendation of this product by the Agency. In order to protect health and the environment, the Administrator, on his motion, may at any time suspend or cancel the registration of a pesticide in accordance with the Act. The acceptance of any name in connection with the registration of a product under this Act is not to be construed as giving the registrant a right to exclusive use of the name or to its use if it has been covered by others.

This registration does not eliminate the need for continual reassessment of the pesticide. If the EPA determines at any time, that additional data are required to maintain in effect an existing registration, the Agency will require submission of such data under section 3(c)(2)(B) of FIFRA.

The product is registered in accordance with FIFRA section 3(c)(5) and is subject to the following terms and conditions:

1. Submit and/or cite all data required for registration of your product under FIFRA section 3(c)(5) and section 4 when the Agency requires all registrants of similar products to submit such data.
2. Submit within 1 year of the date of registration acceptable data packages for Guideline Studies: OPPTS 830.6320 (Corrosion Characteristics) and OPPTS 830.6317 (Storage Stability).
3. Make the following label change before you release the product for shipment: Revise the EPA Registration Number to read, "EPA Reg. No. 73049-460."
4. Submit two (2) copies of the revised final printed labeling before you release the product for shipment. Refer to the A-79 enclosure for a further description of the final printed label.

A stamped copy of the label is enclosed for your record.

Signature of Approving Official:

Keith A. Matthews, Acting Director
Biopesticides and Pollution Prevention Division

Date: 28 February 2012

EPA Form 8570-6

S-Abscisic Acid, Technical Grade Active Ingredient (S-ABA, VBC-30054)

FOR FORMULATION INTO PLANT GROWTH REGULATOR (PGR) PRODUCTS

FOR MANUFACTURING OR FORMULATION USE ONLY

Active Ingredient	
S-Abscisic Acid	99.3% w/w
Other Ingredients	0.7% w/w
Total	100.0% w/w

KEEP OUT OF REACH OF CHILDREN
CAUTION

FIRST AID	
If in Eyes	• Hold eye open and rinse slowly and gently with water for 15-20 minutes. • Remove contact lenses, if present, after the first 5 minutes, then continue rinsing eye. • Call a poison control center or doctor for treatment advice.
HOT LINE NUMBER	
Have the product container or label with you when calling a poison control center or doctor, or going for treatment. You may also call toll-free 1-800-892-0099 (24 hours) for emergency medical treatment and/or transport emergency information. For all other information, call 1-847-968-4700.	

EPA Registration No. 73049-460
EPA Establishment No.

Valent BioSciences Corporation
870 Technology Way
Libertyville, IL 60048
1-847-968-4700

Net Content: 25 kg, 50 kg

ACCEPTED
FEB 28 2010

Under the Federal Insecticide, Fungicide, and Rodenticide Act, as amended, for the pesticide registered under EPA Reg. No. 73049-460

PRECAUTIONARY STATEMENTS

HAZARDS TO HUMANS & DOMESTIC ANIMALS

CAUTION: Causes moderate eye irritation. Avoid contact with eyes or clothing. Wash thoroughly with soap and water after handling and before eating, drinking, chewing gum, using tobacco or using the toilet. Mixers, loaders and handlers must wear the appropriate personal protective equipment (PPE): long sleeved shirt and pants, shoes and sock, and protective eyewear. Remove and wash contaminated clothing before reuse.

ENVIRONMENTAL HAZARDS

Do not discharge effluent containing this product into lakes, streams, ponds, estuaries, oceans or other waters unless in accordance with the requirements of a National Pollutant Discharge Elimination Systems (NPDES) permit and the permitting authority has been notified in writing prior to discharge. Do not discharge effluent containing this product to sewer systems without previously notifying the local sewage treatment plant authority. For guidance contact your State Water Board or Regional Office of the EPA. Do not contaminate water when disposing of equipment wash-waters or rinsate.

DIRECTIONS FOR USE

It is a violation of Federal law to use this product in a manner inconsistent with its labeling.

S-Abscisic Acid is intended for use in the formulation of Plant Growth Regulator (PGR) products, to be applied to field and container-grown plants to induce and regulate PGR responses.

This product may be used to formulate products for any additional uses not listed on the MP label if the formulator has complied with U.S. EPA data submission requirements regarding the support of such uses. Products made from this technical material will require registration with the U.S. Environmental Protection Agency (EPA).

STORAGE AND DISPOSAL

Do not contaminate water, food or feed by storage or disposal.

Pesticide Storage: Keep container tightly closed when not in use. Store product in a cool and dry place. Avoid extended storage conditions at temperatures above 25°C (77°F).

Pesticide Disposal: To avoid wastes, use all material in this container according to label directions. If wastes cannot be avoided, offer remaining product to a waste disposal facility or pesticide disposal program (often such programs are run by state or local governments or by industry). Do not contaminate water when disposing of equipment wash-water or rinsate. Improper disposal of unused pesticide, wash-water or rinsate is a violation of federal law.

Container Disposal: Non-refillable container. Do not reuse or refill this container. Triple rinse container (or equivalent) promptly after emptying. Triple rinse as follows: Completely empty drum liner by shaking and tapping sides and bottom to loosen clinging particles. Empty residue into manufacturing equipment. Fill ¼ full with water. Shake for 10 seconds. Pour rinsate into manufacturing equipment or a mix tank or store rinsate for later use or disposal. Drain for 10 seconds after the flow begins to drip. Repeat this procedure two more times. Then offer for recycling if available or puncture and dispose of in a sanitary landfill, or by incineration. Do not burn, unless allowed by state and local ordinances.

Non-refillable container. Do not reuse or refill this container.
Triple rinse container (or equivalent) promptly after emptying. Triple rinse as follows: Completely empty drum contents into manufacturing equipment or a mix tank by shaking and tapping sides and bottom to loosen clinging particles. Fill container ¼ full with water. Replace and tighten closures. Tip container on its side and roll it back and forth, ensuring at least one complete revolution, for 30 seconds. Stand the container on its end and tip it back and forth several times. Turn the container over onto its other end and tip it back and forth several times. Empty the rinsate into application equipment or a mix tank or store rinsate for later use or disposal. Repeat this procedure two more times. Then offer for recycling if available or puncture and dispose of in a sanitary landfill, or by incineration. Do not burn, unless allowed by state and local ordinances.

Warranty and Disclaimer Statement:
To the fullest extent permitted by law, seller makes no warranty, express or implied, of merchantability, fitness or otherwise concerning use of this product other than as indicated on the label. User assumes all risks of use, storage or handling not in strict accordance with accompanying directions.

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

MEMORANDUM

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

SUBJECT: Consideration of an unconditional registration of the new active ingredient S-Abscisic Acid (PC Code 27200), EPA File Symbol 73049-UAE, for a first food use, Pesticide Petition (PP)# 8F7391. S-Abscisic Acid is a plant regulator intended for use on agricultural crops.

---------- **DECISION MEMORANDUM** ----------

FROM: Keith A. Matthews, Acting Director
Biopesticides and Pollution Prevention Division

TO: Steven Bradbury, Ph.D., Acting Director
Office of Pesticide Programs

ISSUE

Should the Agency grant an unconditional registration under FIFRA § 3(c)(5) for the new biochemical active ingredient S-Abscisic Acid (PC Code 272000) for use in or on all food commodities (PP# 8F7391)? The pesticide product (EPA File Symbol 73049-UAE) is intended for use as a plant regulator, aiding in stress resistance and helping to control fruit set, ripening and senescence.

APPLICATION INFORMATION

On March 16, 2009, EPA published in the Federal Register (Volume 74, Number 49) a notice announcing that Valent Biosciences Corporation, 870 Technology Way, Libertyville, IL 60048, submitted an application to register a pesticide product (EPA File Symbol 73049-UAE) containing a new active ingredient S-Abscisic Acid not included in any currently registered products. On May 6, 2009, EPA published in the Federal Register (Volume 74, Number 86) a notice announcing that Valent Biosciences Corporation, 870 Technology Way, Libertyville, IL 60048, submitted an application proposing to establish an exemption from the requirement of a tolerance for residues of the biochemical pesticide S-Abscisic Acid (ABA) in or on all food commodities (PP# 8F7391). In addition, on January 26, 2010, EPA provided the opportunity for a 30-day comment period on the Agency's draft risk assessment and intention to register this pesticide product. No substantive comments were received following the publication of either notice or during the course of EPA's Public Participation Process.

BACKGROUND AND CONCLUSIONS

The Biopesticides and Pollution Prevention Division (BPPD) reviewed available and submitted data and information regarding the proposed use of ABA.

Evaluations of the data and conclusions are summarized and discussed in the attached Biopesticide Registration Action Document (BRAD).

ABA is well recognized as a plant hormone naturally present in all vascular plants, algae and fungi. It is a regular component of any human diet that includes fruits and vegetables. There have been no observed toxicological effects associated with our long history of consumption of ABA. As a biochemical active ingredient, ABA takes form as a white odorless powder. It is suspended in a sprayable liquid solution and applied directly on plants. ABA has both a non-toxic and a preventative mode of action. It works as a signal agent, helping plants to mediate their developmental processes in the face of stress. Specifically, it serves plants by modulating water uptake, tempering plant growth and fruit set, and by slowing plant metabolism at times when such plant functions would be counter-productive. ABA residues biodegrade rapidly and are not expected to be detectable beyond natural background levels at the time of harvest.

BPPD has also considered ABA in light of relevant safety factors in the Food Quality Protection Act (FQPA) of 1996 and under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) and determined there will be no unreasonable adverse effects from the use of this product. BPPD has considered available data on ABA, including its natural occurrence in edible plants, its nontoxic mode of action, its rapid biodegradation, and the lack of reported adverse effects with regard to its natural consumption. BPPD has concluded that end use products containing ABA can be used without causing unreasonable adverse effects to humans or the environment.

The data submitted by applicant and reviewed by BPPD support the application to register the end use product containing the new biochemical active ingredient S-Abscisic Acid, when used as directed on the label.

OFFICE DIRECTOR CONCURRENCE

Based on the discussion above and the summarized data evaluations in the attached BRAD, BPPD recommends that the new biochemical active S-Abscisic Acid (PC Code 272000) is eligible for unconditionally registered under 3(c)(5) of FIFRA.

Concurrence: Steve Bradley

Non Concurrence: _____

Date: 2/25/10

NEW ACTIVE INGREDIENT REGISTRATION APPLICATION CHECKLIST

Name of active ingredient: ABA

EPA File Symbol/Reg. No. of product reviewed: 73049-UAN, PP# 8F7391

Date: 2/17/10

Note: If a section is not applicable to the application you are reviewing, write N/A.

NEW ACTIVE INGREDIENT SCREEN (ADMINISTRATIVE)

Did the application pass front end and PR Notice 86-5 screens? **If yes, enter into OPPIN, and proceed to do the RAL (PM) screen** **If no, transfer deficient data to Team Leader.**	**YES**

NEW ACTIVE INGREDIENT SCREEN (RAL/SCIENCE)

1. Is the Application Form dated, signed and complete?	**YES**
2. Has the biochemical classification committee made a decision on classification and/or data requirements?	**YES**
3. Is proposed use a food or feed use?	**YES**
If yes, is there a petition for residue tolerance or exemption?	**YES**
4. Are all data requirements, as listed in 40 CFR adequately addressed?	**YES**

DATA REVIEW

1. Data segregated according to discipline	**YES**
2. Data package bean sheets created in OPPIN for each discipline	**YES**
3. Adequate instructions written in bean sheet for science reviewer	**YES**
4. Efficacy data needed for public health uses	**NO**

RAL PRELIMINARY DECISION

1. Look over science reviews	**YES**
2. Additional data needed; if so, request it in a letter	**NO**
3. Label review	
a) Agree with current Label Review Manual	**YES**

b)	Acute toxicology, product chemistry, and efficacy data examined for labeling	YES
c)	Nominal concentration of a.i. listed in ingredients statement (chemist's responsibility)	YES
d)	Storage and disposal instructions agree with container types listed on application form	YES
e)	Directions for use agree with container sizes on application form	YES
4.	Confidential Statement of Formula review.	
a)	Completely filled out including pH, flashpoint, flammability, etc., if applicable	YES
b)	Totals are accurate (everything adds up to 100%)	YES
c)	Certified limits agree with 40 CFR 158.175 or 5 batch analysis	YES
d)	PC codes assigned on CSF for inerts and 40 CFR 180.910-960	YES
e)	No inerts on list 1 present	YES
f)	CSF is signed (original) and dated	YES
5.	Prepare a Biopesticide Registration Action Document (BRAD)	YES
6.	Prepare Plain English Fact Sheet (PEF) -	YES
7.	Prepare Final Rule for tolerance establishment	YES
8.	Route draft Final Rule for science reviewers, OGC concurrence (Note: OGC has two weeks to review)	YES
9.	Prepare Decision Memorandum from Associate Division Director To Office Director for signature	YES
10.	Send the whole package containing: DECISION MEMORANDUM, concurrence sheet, draft label(s), PEF, and BRAD for Branch Chief & DD concurrence, and OD's signature	YES
11.	OD signs off on Biopesticide Registration Action Document and Final Rule; Final Rule published	In Process
12.	Prepare Notice of Registration for DD's signature	YES

BASIC CHECK LIST FOR CONFIDENTIAL STATEMENT OF FORMULAS (CSF)

Please note that if you have any questions at any point, especially with chemical or microbial names, consult with a chemist/ product characterization scientist. It may be helpful to make a copy of the CSF for marking comments, questions, and needed corrections. Upon completion of this form, consult the above scientists. And have them check over the CSF along with your comments.

EPA Reg#/ File Symbol: 73049-UAN (460) CSF(s) dated: 2/24/10 REVIEW DUE DATE: 2/24/10

1. Compare CSF with prior CSF(s), and determine what is different.
Notes: NA

2. Examine label. Does this product have food or feed use sites? Yes.

3. Is each field filled out on CSF? ☑yes ☐ no
Missing: NA

4. Is box 18 signed? ☑yes ☐no

5. Are addresses complete, including zipcodes in boxes 1, 2, and 11? ☑yes ☐no
Deficiencies:

6. Have they enclosed a Material Safety Data Sheet (MSDS) for each new ingredient?
☑yes ☐no
Deficiencies: NA.

7. In column 10. for each component is the chemical name, trade name and CAS No. listed? Is it clear what each component is? For any microbial ingredient, in column 10 - the description should include Colony forming units per gram (CFU/g) and cell collection identity number (E.g. ATCC 889-34.) ☑yes ☐no
Deficiencies: NA. Everything is accounted for.

8. Using a chemical catalog, or Refs verify the CAS #, and chemical name for each component under consideration. Also Note any toxicological information disclosed in catalog.
Deficiencies: NA. CAS#s are correct.

9. Determine PC codes for each component and write these in "EPA USE ONLY" column. Does each component have a PC Code? If code(s) are not found, it may be necessary to send request form to RD. ☑yes ☐no

10. For each inert component determine whether it is listed under 40 CFR 180.1001 (910-960). And write these codes in "EPA USE ONLY" column. (Names may be confusing- consult with a chemist if needed) *If this product is for feed or food use, all inert ingredients **MUST** have appropriate clearance.*
Deficiencies: No inerts. Impurities all clear.

11. For each inert component that does not have 40 CFR clearance determine whether it is a list 1, 2, 3, 4(a) , or 4(b) inert. Write this information in"EPA USE ONLY" column. References to consult: www.epa.gov/opprd001/inerts and FR Vol. 63, No. 121 pages 34384-34390. If any of the inert ingredients are listed as "No longer used" in the above FR vol.63 notice, or are on list 1 or 2, this is a problem to bring attention to chemist.
Problem inerts? NA. Impurities Clear.

12. If product used on food or feed, confirm active ingredient(s) has an established tolerance or exemption from food tolerance. (Consult Alphabetical listing in part 180 of 40 CFR pages 296-300, or the pesticide petition file jacket) ☐ yes ☑ no
Deficiencies: 180.1281.

13. Do certified limits for EACH component agree with 40 CFR 158.175?

Amount in Column 13 b.	Prescribed limits	Upper Limit	Lower Limit
≤1%	N ± 10%N	N x 1.1	N x 0.9
>1% but ≤20%	N ± 5%N	N x 1.05	N x 0.95
>20%	N ± 3%N	N x 1.03	N x 0.97

N= amount in Column 13 b. = nominal concentration

Calculate upper and lower limits using table above and compare with those listed in columns 14 a. and 14 b. of submitted CSF. If they do not agree, identify difference(s): Every calculation is within the limits.

14. Does the sum of the numbers in column 13. a. equal total listed in box 17?
☑ yes ☐no

15 Does column 13. b. add up to 100%? ☑ yes ☐no

16. If Alternative Formulation box is checked in box A- Is there another CSF for a Basic Formulation on file?? ☐yes ☐no ☑NA

17. Other issues? No.

Label Review

File Symbol: 73049-UAN (460) **Date:** 2/24/10 **Reviewer:** Chris Pfeifer

Site/Use	[Res /Ag /Both] [Food /Non-Food /Both]				
Tox Categories: (W)aived	[AcOral: 4 /AcDerm: 4 /AcInhl: 4 /EyeIrr: 3 /SkinIrr: 4 DermSens: N]				
Label Requirement	**Acceptable**	**Not Acceptable**	**N/A**	**Comments Recommendations**	**LRM3**
Restricted Use Pesticide	----------	----------	-----		**Ch 6**
Product Name	✓				Pg 12-3
Compny Name and Info	✓				Pg 15-1
Identification Numbers	✓				**Ch 14**
Net Contents	✓				**Ch 17**
Ingredients Statement	✓				**Ch 5**
Label Claims	✓			Edited	**Ch 12**
Alternate Formula			✓		5-12

Precautionary Statements

Label Requirement	**Acceptable**	**Not Acceptable**	**N/A**	**Comments Recommendations**	**LRM3**
KOROC	✓				3-1 & 9 7-3 & 4
Signal Word	✓				**Ch 3 Ch 7 Ch 10**
General Heading Precautionary Statements	✓				Ch 7
First Aid (PRN 20001-1)	✓			Added	**Ch 3 & 7**
Hazards to Humans and Domestic Animals	✓			Added text	**Ch 3**, 7-3
PPE (WPS) Engineering Controls	✓				Ch 7,Pg 7-12 Pgs 10-4, 15
User Safety Requirements	✓				Ch 10
User Safety Recommendations	✓				Ch 10
Environmental Hazards	✓			Edited	Ch 8
Physical and Chemical Hazards			✓		Pg 3-4 **Ch 9**

Directions for USE (FIFRA Text, WPS plus Storage and Disposal)					
Label Requirement	**Acceptable**	**Not Acceptable**	**N/A**	**Comments Recommendations**	**LRM3**
Header Directions for Use	✓				10-16
Violation of Federal Law text	✓				10-26, **11-7**
WPS Text (PPE)	✓				Ch 10, 7-1 7-11
Non-WPS Text	✓				7-12, **Ch 10**
Storage and Disposal	✓			Edited	11-16, **Ch 13**

Directions for Use (General Instructions and Information)					
Label Requirement	**Acceptable**	**Not Acceptable**	**N/A**	**Comments Recommendations**	**LRM3**
General Instructions and Sub-Header	✓				
Chemigation / Prohibition	✓				PRN
REI	✓				Pg 10-20

Label Requirement	**Acceptable**	**Not Acceptable**	**N/A**	**Comments Recommendations**	**LRM3**
General Info. (non-site specific info. on uses, pests, mixing, and loading, tank mixing, etc.)	✓				
General Precautions and Restrictions	✓				
Directions for Use					
Directions for Application	✓				
Warranty Information					
Consistency with label instructions	✓				12-6
Not false or misleading	✓				

"The warranty section contains an overly broad statement concerning limitations of liability. As such, this statement may be misleading and may constitute misbranding under the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA). It is suggested that the existing statement be preceded by the phrase, **to the extent allowable by state law**, or otherwise qualified to make it clear that this warranty is not intended to be a statement of law which implies that the buyer has no legal rights to recover damages from the manufacturer if he/she suffered a loss or injury from the product and concludes that it would be futile to pursue what might in reality be a valid claim."

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

FEB 2 4 2010

DATE: Feb. 24, 2009.

SUBJECT: Science Review in Support of the Registration of VBC 30054, containing 99.3 % w/w enantiomer S-Abscisic acid, Technical Grade Active Ingredient (TGAI).

Decision Number: 397560
DP Number: 355133
EPA File Symbol Number: 73049-UAN
Chemical Class: Biochemical
PC Code: 272000
CAS Number: 21293-29-8
Active Ingredient Tolerance Exemptions:
MRID Numbers: 474704-01, 474704-03, 474704-06, 474704-10, 474704-11, 474704-12.

FROM: Clara Fuentes, Ph.D. Entomologist
Biochemical Pesticides Branch
Biopesticides & Pollution Prevention Division (7511P)

TO: Chris Pfeifer, Regulatory Action Leader
Biochemical Pesticides Branch
Biopesticides & Pollution Prevention Division (7511P)

ACTION REQUESTED

Valent Biosciences requests registration of 99.3 % w/w enantiomer S-Abscisic acid, Technical Grade Active Ingredient (TGAI), which is a plant growth regulator (PGR) intended for use as manufacturing use product (MP) for formulation of end use products. In support of this registration, the registrant has submitted product chemistry data in MRIDs 474704-01, 474704-03, 474704-06, 474704-10, 474704-11, 474704-12. This is U.S.EPA secondary review in conjunction with Pesticides Programs, APVMA, Australia. All information and data presented in this review were obtained from the APVMA review, unless otherwise noticed.

REVIEWER COMMENTS AND RECOMMENDATIONS

Product chemistry data submitted in support of registration of EPA Reg. No. 73049-UAN are **acceptable**.

A. The following deficiencies were identified by USEPA:

Deficiency # A1: The registrant needs to address Storage stability (OPPTS 830.6317) and Corrosion characteristics (OPPTS 830.6320) for the proposed manufacturing product to satisfy product chemistry data requirements under U.S. Code of Federal Regulation, 40 CFR §158.310. (Physical/Chemical Characteristics are listed in Table 1).

Many deficiencies identified by APVMA concerning identification and purity of the S-ABA TGAI have been adequately addressed in registrant's response to APVMA deficiencies letter, dated June 30, 2009. (Copy of communication letters between APVMA and the registrant, Valent Biosciences, are attached to this review memorandum as reference material).

The registrant has adequately responded to questions about specifications from the 2 batch analyses, and purity profiles as follows:

- The results of specifications from the 5-batches analysis are the most current and the ones that Valent BioSciences will verify.
- The impurities were reduced in the 5-batches analysis.
- Explanations for the higher mass peaks in the mass spectra of S-ABA are found in "Explanations of High-Mass Peaks on the Mass Spectrum of Ascisic Acid" by Daniel Helman.
- The purity of the reference standard was investigated and demonstrated, showing that the standard is S-ABA and there is basically nothing else present in this standard but S-ABA.
- The method used for identification and quantification of impurities [redacted]
- A non-GLP report of chiral HPLC analysis of 5 batches of S-ABA ("*Enantiomeric Purity of 5 abtches of S-ABA determined by Chiral HPLC*," dated 12/7/2007) Study No. BVC-

Manufacturing process information may be entitled to confidential treatment

Manufacturing process information may be entitled to confidential treatment

LG-12-0025) shows [redacted]

B. The following deficiencies were identified by APVMA and addressed by the registrant to EPA satisfaction:

B1. Deficiency: Specifications of S-abscisic acid were generated from a single batch by Lomon Biotechnology Co. Ltd., and from five batch analyses by US Laboratory (PTRL West Inc.). The registrant should clarify which is the specification that applies to the technical S-abscisic acid proposed for registration. (Tables 2 and 3 refer to S-ABA specifications for one and five batch analyses, respectively).

Registrant clarified that 5 batch analysis was submitted and classification is acceptable.

B2. Deficiency: The registrant is requested to provide some analyses of batches of the technical active ingredient to confirm its optical purity i.e., the proportions of the S and R enantiomers. The HPLC methods for determination of purity of the active ingredient do not provide any confirmation of the stereochemistry of abscisic acid, as the methods do not use a chiral column to separate the two enantiomers. The measurement of the specific optical rotation of S-abscisic acid is acknowledged, however this measurement only appears to have been conducted for a batch of the material used as a reference standard (99.7% purity). The registrant is asked to conduct the batch analysis on the technical material proposed for registration. (Tabulated data for five batch, and one batch analyses are presented in tables 4 and 5, respectively).

Registrant has responded that the chiral HPLC analysis of 5 batches shows a [redacted] for all batches.

B3. Deficiency: The registrant should clarify the interpretation of the findings for determination of structurally related impurities of the active ingredient. According to the sample chromatograms for [redacted]

This deficiency has been resolved to EPA satisfaction. All impurities have been identified as [redacted] on the CSF, and they are less than 0.10 %.

STUDY SUMMARIES

Product Chemistry

S-Absisic acid is an essentially non-volatile white odourless solid, slightly soluble in water, highly soluble in polar organic solvents, slightly soluble in aromatic non-polar organic solvents and essentially insoluble in aliphatic non-polar solvents. It has a $\log_{10}P_{OW}$ value of 1.8 and 0.94 in the unionised and ionised forms respectively and as a result is not likely to be fat soluble or to bio-accumulate. It decomposes with melting at 159.2-162.2 °C. As its name suggests, it is a weak acid with a pK_a of 4.61. No hydrolysis was observed in preliminary experiments over 5 days at 50 °C at pH 7 and 9. Very slow hydrolysis (half life > 2 years) was observed in pH 4 buffer at 25 °C, with more rapid degradation (half life of 162 days) in pH 4 buffer at 40 °C. *S*-Abscisic acid demonstrates excellent safety properties, as it is not highly flammable, is not heat, friction or shock sensitive and does not undergo self-ignition. It is stable under accelerated storage conditions (14 days at 54 °C), with or without the presence of metals (aluminium or iron shot) or metal ions (aluminium acetate or iron(II) acetate). It is not reduced by zinc metal, but is oxidised by potassium permanganate (a 5% solution). Manganese dioxide is formed as a by-product.

(Manufacturing process is described in the Confidential Appendix).

Table 1. Physico-chemical properties of *S*-abscisic acid

Property	Value	Method reference
Melting point	Did not melt, decomposes	EEC method A.1 and A.2
Temperature of decomposition	159.2-162.2 °C (99.7% purity, 96.2% purity)	EEC method A.1 and A.2
Appearance and odour	White odorless powder (25 °C, 99.7% purity)	OPPTS Guidelines 830.630, 830.6302, and 830.6304.
Density	1.21 g/cm^3 (96.2% purity)	OPPTS Guideline No. 830.7300.
Vapor pressure	<2 x 10^{-6} Pa (25 °C, 99.7% purity active) 5.8 x 10^{-7} Pa (calculated)	OPPTS Guideline No. 830.7950.
Henry's Law constant	4.8 x 10^{-8} Pa m^3/mol	Calculation from vapour pressure and water solubility.
Water solubility (99.7% purity active, 20 °C)	Distilled water: 3192 mg/L pH 4 buffer: 3102 mg/L	Shake flask method.
Solubility in organic solvents (99.7% purity active, 20 °C)	Methanol: 506.8 g/L Acetone: 290.2 g/L Ethyl acetate: 92.175 g/L 1,2-Dichloroethane: 10.95 g/L Xylene: 0.265 g/L Octanol: 54.8 g/L n-Heptane: 0.0057 g/L	OECD Guideline 105/OPPTS Guideline No. 830.7840
Octanol/water partition coefficient (99.7% purity active)	$\log_{10}P_{OW}$ (unionised form) = 1.8 $\log_{10}P_{OW}$ (unionised form) = 0.94	OPPTS Guideline No. 830.7570.

Property	Value	Method reference
Hydrolysis (99.7% purity active,)	pH 4: k (25 °C) = -0.00088 $days^{-1}$ (half life 792 days) pH 4: k (40 °C) = -0.0043 $days^{-1}$ (half life 162 days) pH 7: very slow hydrolysis pH 9: very slow hydrolysis	OECD Guideline No. 111 and OPPTS Guideline No. 835.2110.
Dissociation constant	pK_a = 4.61 (99.7% purity active)	Titration with 0.1M NaOH
pH of solution	3.32 (1% aqueous solution/suspension of 96.2% purity active)	OPPTS Guideline No. 830.7000.
Specific rotation	409.97° (in ethanol, 10.1 mg/mL, 20 °C)	
Flammability	Not highly flammable (97.0% purity active)	EEC method A10
Explosive properties	Not heat, friction or shock sensitive (97.0% purity active)	EEC method A14
Self-ignition temperature	No self heating below 400 °C (97.0% purity active)	EEC method A16
Accelerated storage stability	No significant degradation on storage at 54 °C for 14 days (97.0% purity active)	OPPTS Guideline No. 830.6313
Oxidative/reductive stability	Oxidised by 5% potassium permanganate solution, which was converted to manganese dioxide. No changes observed with zinc metal, carbon dioxide or water. (97.0% purity active)	OPPTS Guideline No. 830.6314
Stability in the presence of metals and metal ions	No significant degradation over 14 days at 54 °C when stored in the presence of aluminium shot, iron shot, aluminium acetate or iron(II) acetate. (97.0% purity active)	OPPTS Guideline No. 830.6313

The physico-chemical properties were determined using suitable test methods, in accordance with the OECD Principles of Good Laboratory Practice (GLP).

S-Abscisic acid specifications: *Specifications for Technical S-abscsic acid.*

Table 2: Specification set 1.
Analyses of a single batch by manufacturer Lomon Biotechnology Co. Ltd.

[redacted]

Manufacturing process information may be entitled to confidential treatment

Pages 103-118 *Manufacturing process information may be entitled to confidential treatment*

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

DEC 1 0 2009

OFFICE OF PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

DATE: Dec. 10, 2009.

SUBJECT: Science Review in Support of the Registration of 99.3 % w/w *S-Ascisic Acid (S-ABA) Technical Grade Active Ingredient (TGAI).*

Decision Number: 397560
DP Number: 355254
EPA File Symbol Number: 73049-UAN
Chemical Class: Biochemical
PC Code: 272000
CAS Number: 21293-29-8
Active Ingredient Tolerance Exemptions:
MRID Numbers: 474705-07 to 474705-13; 474705-14, 474705-15, 474705-16, 474705-17, and 474705-21.

FROM: Clara Fuentes, Ph.D. Entomologist
Biochemical Pesticides Branch
Biopesticides & Pollution Prevention Division (7511P)

TO: Chris Pfeifer, Regulatory Action Leader
Biochemical Pesticides Branch
Biopesticides & Pollution Prevention Division (7511P)

ACTION REQUESTED

Valent Biosciences Co. requests registration of VBC-30054, *S-Ascisic Acid (S-ABA) Technical Grade Active Ingredient (TGAI)*, which is intended for use as manufacturing use product (MP) in the formulation of end use products. In support of this registration, the registrant has submitted subchronic mammalian toxicity in MRIDs 474705-07 to -13; Ecotoxicity data in MRIDs 474705-14 to -17; request for waiving Avian Dietary Toxicity testing requirement, and Multi Residue Testing methods in MRIDs 474705-21 and 474705-22, respectively, and Evaluation of Environmental Safety of S-ABA in MRID 474704-13.

RECOMMENDATIONS AND CONCLUSIONS

1. Tier I Toxicity: Subchronic mammalian toxicity studies:

MRID	OPPTS Guidelines	Study Title	Classification	NOEL
474705-07	Non-guideline	VBC-30054 One Week Dose Range Finding Study in Rats with Dermal Administration	Supplemental	1000 mg/kg/day.
474705-08	870.3200	VBC-30054: 3 Week Toxicity Study in Rats with Dermal Administration	Acceptable pending clarification	1000 mg/kg/day
474705-09	870.3050	VBC-30054: 4 Week Toxicity Study in Rats with Administration by the Diet	Acceptable.	20000 kg/mg
474705-10	870.3100	13 Week Toxicity in Rats with Administration by the Diet.	Acceptable.	20000 kg/mg
474705-11	Non-guideline	VBC-30054 Preliminary Developmental toxicity in Rats	Supplemental.	20000 kg/mg
474705-12	870.3700	A Prenatal Developmental Toxicity Study in Rats.	Acceptable	1000 mg/kg/day

MRID	OPPTS Guidelines	Study Title	Classification	NOEL
474705-13	Non-guideline	VBC-30054 Reporter Gene Assays for Abscisic Acid (ABA) Using Human Estrogen and Androgen Receptors	Acceptable	S-ABA is not an estrogenic, anti-estrogenic, androgenic or anti-androgenic compound.

MRID 474705-07:

- There is little explanation for the information presented on tables and graphs; i.e., no discussion on statistical analysis and interpretation of results.
- There is no sufficient rationale supporting the statement that differences in exposure periods (resulting from treatment removals by some animals, and not immediate reapplications) do not affect the integrity of results.
- The study report does not include information on husbandry, animal age and health conditions.
- Ambient laboratory conditions during the test are not reported.

MRID 474705-08:

The study deviates from US EPA OPPTS 870.3200, *21/28-Day dermal Toxicity,* recommendations as follows:

- For determination of a NOEL, 10 animals per treatment are needed. For screening purposes, only 5 animals per treatment are sufficient. Only 5 animals per treatment were employed in this study for determination of a NOEL.
- Light cycle of 12:12 light: dark is recommended. However, the light cycle in the reported study was 07 – 19 light hours.
- Treatments were arranged to create a dose response curve as recommended by OPPTS guidelines 870.3200. However, the data was not analyzed for statistical significance of response trends.

The registrant should justify choice of sample size, and statistical procedure, and provide rationale for asserting that removal of bandages by some animals is inconsequential.

1. Sample size. Use of 5 rather than 10 animals per treatment as recommended by OPPTS guidelines 870.3200.

2. Statistical procedure. Choice of pairwise comparison rather than regression analyses for significance of response trends.

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3. Bandage removal. The registrant should clarify how animals who removed their bandages were prevented from ingesting the test material, and likely compromise test results.

MRID 474705-09:

The following observation does not constitute a deficiency likely to affect the study results:

- There is no description of randomization procedures for allocation of animals to treatments.
- No detail is provided concerning whether females were nullliparous and nonpregnant.
- Light cycle was 7:19 h. rather than 12:12 hours, as recommended by OPPTS 870.3100 guidelines.

MRID 474705-10:

The study is acceptable. However, the registrant should express NOEL as dosage in mg/kg(BW)/day rater than concentration units (ppm).

The following deviations from OPPTS Guidelines OPPTS 870.3100 do not constitute major deficiencies likely to compromise study results:

- There is no description of randomization procedures for allocation of animals to treatments.
- No detail is provided concerning whether females were nullliparous and nonpregnant.
- Light cycle was 7:19 h. rather than 12:12 hours, as recommended by OPPTS 870.3100 guidelines.

- There is no satellite group as recommended by OPPTS 870.3100 guidelines. A group of 10 males and 10 females, treated at the highest dose should have been observed for no less than 28 days post treatment. There is no indication in the study report that this was done. The reviewer assumes that this was not done due to reported lack of toxicity

- The data may have been analyzed for determination of a trend. Dose treatments are continuous variables that could have been appropriately analyzed using regression analysis to determine whether a dose trend is statistically significant for any of the measured endpoints.

MRID 474705-11: This is a preliminary study. It deviates from OPPTS 870.3700 *Prenatal Development Toxicity Study* recommendations as follows:

- Number of experimental units or treatment replicates, 6 animals per treatment, were below guidelines recommendations of 20 animals per treatment.

- There was no statistical analysis of test results.

It is uncertain whether test results are reliable due to small sample size and lack of statistical analysis.

2. Tier I Non-Targets

MRID 474705-14, *An Acute Toxicity Study with the Earthworm in an Artificial Soil Substrate.*

Classification: Supplemental.
This is a non OPPTS guideline study, conducted according to procedures outlined in OECD Guidelines No. 207. The study is adequate and results are likely to be reliable, except for lack of information regarding homogeneity and stability of test substance in the soil.

- The registrant should verify whether homogeneity and stability of test material in the soil were monitored throughout the study, and describe the procedures employed for doing so.

MRID 474705-15, *Environmental Safety Assessment of Natural Abscisic Acid (Zhu, et al. (2000)).*

Classification: Supplemental and unacceptable due to the following deficiencies:

It is expected that controls were used. The US Ecological Effects Test Guideline OPPTS

850.2100 Avian Acute Oral Toxicity Test requires use of a concurrent control during every test. However, the absence of information on this and whether any control birds died or exhibited adverse symptoms is a most significant deviation from the OPPTS 850. 2100 guidelines. There is also a significant deviation from the OPPTS guidelines in that the Chinese report only refers to the test being run over 96 hours following treatment; OPPTS guideline requires an observation period of at least 14 days. Given the summary nature of the report, it is clearly not possible to know if the OPPTS requirements were met.

MRID 474705-16: *Terrestrial plant toxicity OPPTS Guideline 850.4150 (Tier I Vegetative vigor).*

Classification: Unacceptable.
The test substance was not 99.3 % w/w S-ABA (TGAI) proposed for registration. The test substance was end use product, VBC-30074, containing 10.7 % S-ABA.

MRID 474705-17: *Terrestrial plant toxicity OPPTS Guideline 850.4100 (Tier I Seedling emergence).*

Classification: Unacceptable.
The test substance was not 99.3 % w/w S-ABA (TGAI) proposed for registration. The test substance was end use product, VBC-30074, containing 10.7 % S-ABA.

Deficiency: Not satisfied data requirements OPPTS 4150 (Tier I Vegetative vigor) and OPPTS 850.4100 (Tier I Seedling emergence). Effect of S-ABA (TGAI) on non-target terrestrial plants is required for section 3 registration, and data has not been submitted. The registrant needs to resolve this deficiency to satisfy data requirements for section 3 registration of S-ABA (TGAI).

Particularly important is the assessment of bud development, flowering and fruit setting in non-target plants. The registrant is requested to address the potential phytotoxic effects of S-ABA on these endpoints.

MRID 474705-21: Request for waiving chronic exposure of birds to S-ABA is acceptable. Chronic exposure of birds to S-ABA is expected to be limited as a result of the ready degradation of S-ABA and the limited time of application. No actual test should be required.

MRID 474705-22: Request for waiving Multi Residue testing method (OPPTS Guidelines 860.1360) for S-ABA is acceptable based on existing knowledge of ABA metabolism and natural levels present in the environment.

3. Environmental Fate:

MRID 474704-13, *Environmental Safety Assessment of S-Abscisic acid (Shi, L. (2004)).*

Classification: Unacceptable. To make the study acceptable, the registrant needs to resolve the following deficiencies:

- Lack of information as to whether the study was conducted according to OECD or OPPTS guidelines;
- The uncertainty as to the actual intensity of the ultraviolet light used;
- Lack of certainty with respect to the use of a filtered Xenon lamp; and
- Lack of identification of degradation products formed.
- No methods of analysis for determination of S-ABA in sediment were provided. Details on the properties of the soil used were not provided. Apart from recalculation of the percentage and average recoveries and the relative standard deviation, the summary report did not provide sufficient data for any further validation of the method.

Endangered Species Assessment for S-ABA (TGAI):
Based on the fact that this chemical is not toxic to non-target organisms already tested, and on its use pattern and use instructions, EPA has determined it will have "No Effect" on any currently listed threatened or endangered species or any designated critical habitat, **except for non-target plants, for which data has not been submitted.**

STUDY SUMMARIES

1. Toxicity

MRID 474705-07, *VBC-30054 One Week Dose Range Finding Study in Rats with Dermal Administration,* is a preliminary one week study to assess the dermal toxicity of VBC 30054 (TGAI) on rats. The study was conducted in GLP compliant facility. The study report was amended to include additional data, requested by the Sponsor, on which animals had removed their occlusive bandages during treatment and to clarify that the test item was applied daily.

Four groups of 5 male and 5 female Sprague-Dawley rats were assigned to dose treatments of 0, 10, 100, and 1000 mg/kg/day of test material, VBC-30054, mixed with 0.5% high viscosity carboxymethyl cellulose. The treatments were applied evenly over an area approximately 6 x 6 cm^2 of exposed skin on the lumbar region. A dressing of foil gauze and self adhesive bandage was wrapped around the torso of each animal for approximately 6 h, to prevent oral ingestion. After this period the dressings were removed and the dose area wiped clean with a cloth dampened with distilled water. Applications were repeated daily. The experiment lasted 1 week. All animal were killed after one week of treatment. Ten major organs were weighed and fixed in 10% neutral buffered formalin with the exception of the testes which were fixed in Bouins fluid. Implants were retained to be identified.
General Observations were recorded once during pretreatment, and once during treatment period. Viability was recorded twice daily; body Weights were recorded twice weekly during pretrial and the treatment period; food Consumption was recorded twice weekly during pretrial and the

treatment period, and water Consumption was monitored weekly by visual inspection of water bottles.
After one week treatment, all animals were killed. Ten major organs were weighed and fixed in 10% neutral buffered formalin with the exception of the testes which were fixed in Bouins fluid. Implants were retained for the purpose of identification. Isolated incidences of desquamation and well defined erythema were noted in groups receiving 0, 10 and 100 mg/kg/day. No incidences of desquamation or erythema were noted in the 1000 mg/kg/day group.
Absolute and covariant adrenal gland weight was noted to be slightly lower (not statistically significant) in animals treated at 1000 mg/kg/day when compared to their Controls. Absolute and adjusted ovary weight was also noted to be slightly lower (not statistically significant) in Females receiving 100 and 1000 mg/kg/day when compared to their Controls.
Isolated incidents of desquamation and well defined erythema were observed in groups receiving less than 1000 mg/kg/day dose. No incidences of desquamation or erythema were noted in the 1000 mg/kg/day group. Slight differences in body and organ weights were not significantly different from controls; adrenal gland weights in animals receiving the highest dose, and ovarian weights in females receiving 100 and 1000 mg/kg/day were slightly lower than controls and not significantly different. There were no necropsy findings that were considered to be related to treatments with VBC-30054.
Due to the lack of a dose related response, and lack of significant observations in the high dose group, it was concluded that the clinical signs were not toxicologically significant or treatment related, and the No Adverse Effect Level (NOAEL) is set at 1000 mg/kg/day.

MRID 474705-08, *Three Week Toxicity Study in Rats with Dermal Administration*

The study report was conducted in accordance with the OECD Principles of Good Laboratory Practice which are comparable with the United States of America (EPA) 40 CFR 160 and acceptable to Japan (MHI.W, MAFF, METI). The objective of the study is to evaluate the mammalian toxicity of VBC-30054 Technical Grade Active Ingredient (TGAI) after continuous daily exposure of 6 hours for 21 days in rats. The study was designed in accordance with OPPTS 870.3200 guidance and OECD Guidelines No. 410.

Four groups of 5 male and female Sprage Dawley rats, approximately 7 weeks old, weighing 221-269 g. (males), and 168- 205 g. (females), were randomly assigned to 4 dose treatments (0, 100, 300 and 1000 mg/kg/day of VCB-30054). The animals were received in the laboratory when they were approximately 5 weeks old, and allowed to acclimate for 2 weeks before initiation of the test. The study consisted of 4 completely randomized treatments. Each treatment consisted of increasing doses of VCB-30054 at 0, 100, 300 and 1000 mg/kg/day, applied daily via the dermal route to 5 male and female rats per treatment for a period of 3 weeks. The test material was properly identified and stored. Formulations were prepared daily by mixing appropriate amounts of test material with 0.5% high viscosity carboxymethylcellulose. Concentrations of 0, 50, 150 and 500 mg/ml were examined for stability and homogeneity before being applied to a 2 mL/kg volume to concentration levels of 0, 100, 300 and 1000 mg/kg, respectively. Each testing dose formulation was sampled in triplicates and analyzed for homogeneity and accuracy. Nominal concentrations for testing doses were within acceptable

ranges (around ± 5 %), except for the intermediate dose formulation that was -12 % from nominal on day 1 of treatment.
The lumbar region of the animals was clipped to expose the skin (approximately 6 x 6 cm) with the test formulation being spread evenly over this area. A dressing of foil gauze and self adhesive bandage was wrapped around the torso to prevent oral ingestion. Following 6 hours of exposure the dressings were removed and the dose area wiped clean with a cloth dampened with distilled waterThe lumbar region of the animals was clipped to expose the skin (approximately 6 x 6 cm) with the test formulation being spread evenly over this area. A dressing of foil gauze and self adhesive bandage was wrapped around the torso to prevent oral ingestion. Following 6 hours of exposure the dressings were removed and the dose area wiped clean with a cloth dampened with distilled water.
The animals were housed individually by sex and dose treatment group in suspended polycarbonate cages (42 x 27 x 20 cm) with stainless steel grid tops and bottoms. Water and food were supplied *ad libitum,* except during urine collection. Urine samples were collected from all animals during 3 week period by placing the animals into metabolic cages. Urine samples were collected over 4 hours period. During this time, animals were deprived of food and water. The diet was supplied with a batch analysis for nutrient components and contaminant. Water was also regularly analyzed for dissolved materials, and found acceptable. Rearing conditions in the laboratory were maintained within target ranges throughout the test. Temperature was 19 ° C to 23 ° C, and RH was 40 – 70 %. Photoperiod was 7 to 19 hours cycle. All animals were monitored twice a day for viability, skin condition, good health, body weight, or reaction to treatments before application of the test material, and after 6 hours of daily exposure. Food consumption was recorded twice weekly. Ophthalmoscopy was assessed on all animals in control and high dose groups throughout duration of treatments. All animal were killed at the conclusion of the test, and examined for tissue anomalies. All males and some females at the highest doses, 300 and 1000 mg/kg/day, showed very slight erythema on the application site. Increased in white blood counts were observed in males at the highest dose, 1000 mg/kg/day, and were considered to be of no toxicological significance. Clinical observations included stained fur, discharge from the eye(s), and skin discoloration in some animals treated at 1000 and 300 mg/kg/day doses. Body weights, ophthalmic findings and food consumption showed no notable differences. Increased white blood cell counts and related parameters, were statistically significant due to increased lymphocyte and neutrophil counts, specially in males at the highest dose treatment. These values were lower at lower doses sand no dose related trend was observed. No significant differences were reported for clinical chemistry and urinalysis endpoints. No significant differences were reported for body and organ weights. Necropsy and histology findings were not no statistically significant, and no attributable to treatments. The slight erythema noticed at the dose site for animals at 1000 mg/kg/day dose treatment, and some animals treated with 300 mg/kg/day dose were considered due to normal irritation and not systemic toxicity. It was concluded that increments in white blood cells and associated parameters with no corroborating histological findings indicated that these changes were no toxicologically significant. In conclusion, the higher dose treatments were associated with very slight erythema for both sexes, and increased white blood cell counts and related parameters in males at the highest dose. These results were attributed to the route of administration rather than to treatments and not considered toxicologically significant.

Statistical analysis consisted of 2-sided pairwise comparisons of each dose treatment against control. Level of significance was set at $P \leq 0.05$. Males and females were analyzed separately. The tested endpoints were body weight, food consumption, hematology, clinical chemistry, and urinalysis data. Variance was found homogenous, and ANOVA was used for determination of statistically significant effects due to treatments. Pairwise comparisons were performed only if the overall F-test was significant.

There were no histological findings and thus, the No Observed Adverse Effect Level (NOAEL) is set at 1000 mg/kg/day.

MRID 474705-09, *VBC-30054: Four Week Toxicity Study in Rats with Administration by the Diet*

The objective of the study wass to assess the oral toxicity of VBC-30054 (Technical grade S-Abscisic Acid (ABA) administered via oral route for 4 weeks. This study was designed in compliance with the guidelines of the EU authorities, and is in accordance with the guidelines detailed in the OECD 407 (adopted by the council on 21 September 1998) and OPPTS 870.3050 (July 2000) of the US EPA.

Four groups of 5 male and 5 female Spraque-Dawley rats were dosed continuously by diet for 4 consecutive weeks at levels of 0, 2000, 6000 and 20000 ppm. S-ABA. Animals were randomly allocated to 4 dose treatment of 0, 2000, 6000 and 20000 ppm. S-ABA. The animals were dosed by oral administration for 7 days/week for 4 consecutive weeks. Control animals received blank diet only. The rats were regularly monitored for any signs of ill health or reaction to treatment throughout the study. Detailed functional observations were performed weekly, with additional functional investigations performed during pretrial and at week 4 of treatment. Body weight and food consumption were recorded at regular intervals until the end of the treatment. Blood and urine samples were collected for laboratory investigations at the end of treatment.
On completion of the 4 weeks treatment, all animals receiving 0 and 20000 ppm were subjected to necropsy.
Diet formulations were prepared weekly, and analyzed in triplicate samples for concentration, homogeneity and stability. The concentrations of the formulations were within ± 5% of the nominal, indicating acceptable accuracy of formulation. The low coefficients of variation indicate satisfactory homogeneity. Concentrations in the diet were constant throughout the treatment period. Blank diet, without S-ABA, was prepared for control animals.
Animal husbandry and ambient conditions were reported and found adequate. There was automatic control of temperature and humidity. Target ranges were 21°C ± 2°C and RH= 55% ± 15, with a minimum of 15 air changes per hour. It is reported that there were 2 occasions during Week 3 where the humidity was below the target humidity range, but this was considered not to have adversely affected the rats. Light hours were 0700-1900 h. cycle.

Statistical procedures for data analysis were described in detail. All statistical tests were two-sided and performed at the 5% significance level using in-house software. Males and females

were analysed separately. Pairwise comparisons were only performed against the control group. Body weight, hematology, clinical chemistry, selected urinalysis and selected neurotoxicity data were analyzed for homogeneity of variance using the 'F-Max' test. If the group variances appeared homogeneous, a parametric ANOVA was used and pairwise comparisons were made using Fisher's F protected LSD method via Student's test ie pairwise comparisons were made only if the overall F-test is significant. If the variances were heterogeneous, log or square root transformations were used in an attempt to stabilize the variances. If the variances remained heterogeneous, then a Kruskal-Wallis non-parametric ANOVA was used and pairwise comparisons were made using chi squared protection (via z tests, the non-parametric equivalent of Students's t test).
In circumstances where it was not possible to perform the F Max test due to zero standard deviation in at least one group, the non-parametric ANOVA results were reported.
Organ weights were analyzed using ANOVA as above and by analysis of covariance (ANCOVA) using terminal kill body weight as covariate. In addition, organ weights as a percentage of terminal body weight were analyzed using ANOVA as above as an exploratory analysis, but not reported.
In circumstances where the variances in the ANCOVA remained heterogeneous following log or square root transformations or where it was not possible to perform the F-Max test, the untransformed parametric ANCOVA results were reported.
Histological incidence data were analyzed using Fisher's Exact Probability Test.

There were no premature deaths during the study. There were no clinical observations that could be attributed to treatment with VBC-30054.
There were no notable intergroup differences in neurotoxicity clinical observations in either sex that were attributed to treatments effects.
There were no notable intergroup differences in motor activity in either sex that were considered treatment related.
There were no notable intergroup differences in detailed functional observations in either sex that were attributed to treatment.

After 4 weeks of dose treatments, group mean body weight gain and group mean body weight were slightly lower in males treated at 20000 ppm when compared to controls, but were not statistical significant. Administration of VBC-30054 via the diet for 4 consecutive weeks was associated with slight reductions (without statistical significance) in mean body weight gain in both males and females treated at 20000 ppm only. No notable findings were seen in males and females treated at 2000 and 6000 ppm. There was no effect on food consumption (Tables 19 and 20, Appendices, 26 and 27). There were sporadic incidences where the food consumption in treated groups was higher or lower when compared to their respective controls, however no pattern was established and therefore was not attributed to treatment effect. There were no findings that could be attributed to treatment of VBC-30054 (Appendix 28). Mean cell hemoglobin was slightly reduced in males treated at 20000 ppm when compared to controls. Reticulocytes in females were statistically significantly lower in all treated groups however no dose related pattern was seen. White blood cell parameters such as lymphocytes and neutrophils were slightly lower (without statistical significance) in males treated at 20000 ppm when compared to the controls. Females treated at 20000 ppm had slightly lower lymphocytes without

statistical significance when compared to the controls. Neutrophils were statistically significantly lower in all treated female groups when compared to the controls, but this was attributed to two high control values.
Activated partial thromboplastin time was slightly lower in males treated at 20000 ppm with statistically significance.
No notable findings were seen in any other hematological parameters in animals treated at 2000 and 6000 ppm.
Urea was slightly lower in males and females treated at 20000 ppm when compared to their respective controls, but the difference was not statistically significant. Glucose was noted to be statistically significantly lower in males than the controls in a dose related pattern.
No notable findings were seen in any other clinical chemistry parameters.
Specific gravity in males treated at 20000 ppm was slightly lower when compared to the controls, but it was not statistically significant.
Covariant epididymide weights were slightly higher in males treated at 2000 and 6000 ppm in comparison to the controls with statistical significance. Testes weights were slightly higher at 20000 ppm without statistical significance. Males treated at 6000 ppm and above had slightly increased covariant salivary gland weights without statistical significance.
Covariant salivary glands and thyroid glands were slightly increased in females treated at 20000 ppm in comparison to the controls, both without statistical significance. Females treated at 2000 ppm also had higher kidney weights with statistical significance when compared to the controls, however no other notable findings were seen in the other treated groups.
There were no necropsy findings s at any dose level that were attributed to dose treatments with VBC-30054. All necropsy findings were considered typical of spontaneous arising histological findings in rats of this age and strain.
There were no histological findings at any dose level that were attributed to treatments.
All histological findings were considered typical of spontaneous arising histological findings in rats of this age and strain.

The researcher concluded that administration of VBC-30054 via the diet for 4 consecutive weeks was associated with slight reductions (without statistical significance) in mean body weight gain in both males and females treated at 20000 ppm only. There was no effect on food consumption. The slightly lower values without statistical significance of selected white blood cell parameters in males and slightly lower urea in males and females with lower glucose (with statistical significance) in males were only seen in animals treated at 20000 ppm and were not thought to be of toxicological significance due to the lack of any contributing necropsy and histological findings. Very slight effects seen in reticulocytes and white blood cell parameters in all treated groups were considered to be due to higher than expected control values. Furthermore, there were no neurotoxic findings that were attributed to dose treatments.
Under the conditions of this study, the researcher established No Observed Adverse Effect Level (NOAEL) at 20000 ppm.

MRID 474705-11, *Preliminary Developmental Toxicity in Rats*.

The purpose of this study was to estimate the maximum tolerable dose of VBC-30054 in the diet

of pregnant females and their fetuses. The test animal was the rat because it is a standard rodent species representative of mammals, and required by regulatory authorities in the United Kingdom, where the study was conducted. The dietary route was chosen for administration of the test substance because this is the likely route of exposure in humans.

Groups of six mated female Sprague-Dawley rats were randomly assigned to 3 treatment groups, including control. Each treatment consisted of dose levels of 0, 10000, and 20000 ppm. of VBC-30054 Technical. The rats were 9 weeks of age when mated. No more than one female was mated by any one male. All animal were examined prior to testing and found healthy. The rats were 9 weeks of age when mated. No more than one female was mated by any one male. All animal were examined prior to testing and found healthy.
The animals were continually dosed orally via their diets from day 6 to day 20 of gestation period. Day 6 of gestation was considered day of implantation, occurring 6 days after day of mating.
Diet formulations were prepared in one occasion by mixing required amounts of VBC-30054 with required amounts of blank diet for 20 minutes, sealed and refrigerated. They were analyzed for homogeneity in triplicate samples of 50 g. immediately following preparation. The blank diet was supplied with an analytical certificate of nutritive constituents and contaminants. Analysis of dosing formulations showed a low coefficient of variation (< 1.5%), indicating that the formulations were homogenous.
Rearing conditions were within acceptable range, except for humidity which was 26 to 57 % instead of the target range 55 ±15 % on seven occasions. Study results were considered not to be affected by these deviations. Rats were housed in individual cages made of polypropylene (42 x 27 x 20 cm). Water was provided *ad libitum*, and analyzed for dissolved materials. Water and bedding, made of sterilized wood shavings, were provided and changed regularly.
Animals were observed for viability twice a day, early morning and late evening, and examined for any reactions to treatments. Body weights were recorded on days 4, 6, 9, 13, 17 and 20 of gestation. The achieved intake of S-ABA was calculated using the following formula:

Achieved Intake = (Mean Food Consumption x Dietary nominal Concentration) / Mean Body Weight.

All animals were killed on day 20 and examined for necropsy, number of corpora lutea graviditatis per ovary, and number and position of implantation sites in the uterus. Each fetus was weighed and examined for external visible abnormalities.

There were no clinical signs or necropsy findings at doses up to 20000 ppm. At doses 10000 and 20000 p.pm., there was slight reduction in body weight gains over Days 17-20 of gestation; it was not clear that these weight reductions were related to treatments. Slight intergroup differences in pregnancy and fetal weights were too small to be treatment related. The dose levels up to 20000 p.p.m of VBC-30054 show no developmental toxicity effects in rats.
At 20000 p.p.m., pregnancy performance was comparable to control. At 10000 p.p.m., the slight increase in early embryonic deaths was mainly due to one animal, assuming that this early death was incidental. Intergroup differences in fetal weights were too small to be attributable to treatments.

No formal statistical analysis was performed because it was not considered necessary.

Based on these preliminary results, it is concluded that dose level up to 20000 p.p.m. in food do not show adverse effects of developmental toxicity in rats.

MRID 474705-12, *Prenatal Developmental Toxicity Study in Rats.*

The objective of the study is to evaluate the potential of VBC-Abscisic acid Technical Grade Active Ingredient to induce developmental toxicity after maternal exposure during the critical period of organogenesis, and characterize maternal toxicity to determine a no adverse effect level (NOAEL).
The study was conducted consistently with OPPTS guidelines recommendations 870.3700.

Three dose levels (500, 750, and 1000 mg/kg/day) of VBC-30054 were assigned to separate groups of 25 female rats per group. The doses were within ± 2% of their nominal concentrations, and stable for 10 days of refrigerated storage. A fourth control group of 25 females received a comparable treatment of 0.5% methylcellulose with no VBC-30054. The number of animals used for testing was based on US EPA Health Effects Test Guidelines OPPTS 870.3700, Prenatal Developmental Toxicity Study (1998), and OECD Guidelines for Testing of Chemicals Guidelines 414, Prenatal Development Toxicity Study (2001). The experiment was a randomized block design consisting of 4 dose treatment groups, including one control group, of 25 females each. Females were stratified by body weights on their gestation day 0 and randomized into blocks.
The rats were approximately 70 days old when received in the laboratory, and 90 days old at initiation of the test. Females were selected for the test based on acceptable health and weight. The selected females were approximately 12 weeks old when paired for breeding. Mating was confirmed by presence of vaginal copulatory plug or sperm. Doses of VBC-30054 in 0.5% methylcellulose were administered orally once a day via gavage at a dose volume of 10 mL/kg, from gestation days 6 to 19. All animals were killed on day 20 for further examination.
All animals were observed twice daily for vitality, once in the morning and once in the afternoon during duration of the test. Animals were also monitored 1 hour following dose administration. Clinical observations, body weights and food consumption were recorded. On gestation day 20, a laparohysterectomy was performed on each female. Uteri and ovaries were examined, and the number of fetuses, early and late resorptions, total implantations, corpora lutea, gravid uterine weights and net body weights were recorded. The fetuses were examined for malformations and developmental variations. All observations were recorded blind of test group.
Treatments were compared to control using 2-tailed tests when overall F was significant in a one way ANOVA analysis. Each mean was reported with its associated standard deviation and standard error. Fetal endpoints measured were analyzed using Kruskal-Wallis nonparametric ANOVA procedure. Minimum significance levels were set at $P \leq 0.01$ and 0.05 % .
No dose related effect on maternal body weight, food consumption, post implantation losses, size of live litters, mean fetal weight, fetal sex rates, fetal malformations or developmental variations were observed to be attributed to dose treatments. Based on these results, NOAEL level was set at 1000 mg/kg/day.

MRID 474705-13, *VBC-30054 Reporter Gene Assays for Abscisic Acid (ABA) Using Human Estrogen and Androgen Receptors*:

This is a non-guideline *in vitro* test to evaluate estrogenic, anti-estrogenic, androgenic and anti-androgenic effects of ABA using mammalian cell-based luciferase reporter.

Estrogenic, anti-estrogenic, androgenic and anti-androgenic activities of absicic acid were evaluated using receptor- mediated assays in vitro. Mammalian cell-based luciferase reporter gene assays were developed for detecting the effects of ABA on human estrogen receptor α (hERα) or androgen receptor (hAR) mediated transactivation. Cells expressing luciferase constitutively were used for estimating effects of chemicals on transcriptional activity by a receptor-independent manner or cytotoxicity.
Marked positive effects of estradiol (E2) and dihydrotestosterone (DHT) were detected by hER α and hAR assays, respectively. Anti-estrogen, 4-hydroxytamoxifen (HTM) and anti-androgen, hydroflutamide (HFT) inhibited the E2 and DHT-mediated transactivation, respectively. Differences were tested for statistical significance at $p < 0.05$, using t-test computed by Excel (Microsoft). However, no significant estrogenic, anti-estrogenic, androgenic or anti-androgenic effect of ABA was found by the assays (1 nM-10 μM), suggesting that ABA does not impact on hER α and hAR-mediated transactivation pathways in vitro.
Following exposure to E2 (1 μM), cells transfected with hER α showed induction of about 12-fold relative to solvent control in the mammalian cell-based luciferase reporter gene assay. No significant ($p < 0.05$) ligand-dependent activations of luciferase was found with S-ABA . Anto-estrogen (4-hydroxytamoxifen) markedly inhibited E2-mediated luciferase inductions. However, no significant effects were detected by treatment with ABA. In these assays, ABA did not show any citotoxicity or transactivational activity in a receptor-independent manner. Cells transfected with hAR showed marked induction of about 70 fold relative to solvent control by treatment with DHT (1 μM). No significant ligand-dependent activation of luciferase was appeared with ABA. Anti-androgen (hydroxyflutamide) markedly inhibited DHT-mediated luciferase inductions. However, no significant effects were detected with ABA. In these assay, ABA did not show any cytotoxicity or transactivational activity in a receptor-independent manner.
These results indicate that ABA is not capable of affecting ER α and AR mediated transcativational in vitro. Therefore, it can be concluded that ABA is not an estrogenic, anti-estrogenic, androgenic or anti-androgenic compound.

2. Non-Targets

Non-Target Data Requirements

Study Type/OPPTS Guideline	LD_{50}/LC_{50}/Results	Toxicity Category	MRID
Avian Acute Oral/OPPTS 850.2100	>2250 mg/kg *	IV	
Avian Dietary/OPPTS 850.2200	Requested data waiver	**	474705-21

Study Type/OPPTS Guideline	LD_{50}/LC_{50}/Results	Toxicity Category	MRID
Freshwater Fish LC50/OPPTS 850.1075	>121 mg./L	IV	
Freshwater Invertebrate/OPPTS 850.1010	>116 mg/L	IV	
Non-target Plants/OPPTS 850.4000	Data is required		No study submitted
Non-target insects/OPPTS 48-hour oral and contact toxicity to honey bees (*Apis mellifera L.*)	>108 µg/bee in the oral toxicity and >100 µg/bee in the dermal (contact) toxicity test		471512-01

* The primary reviewer determined LD50 > 2165 mg/kg and NOEC = 2165 mg/kg based on the purity (96.2 %) of the active ingredient

** No avian chronic or reproductive toxicity studies with S-ABA were presented. S-ABA is not expected to persist in the environment and, consequently, exposure to high levels of S-ABA are likely to be restricted to relatively short periods immediately after spray application and only for a relatively short period. As a consequence, chronic exposure of birds to S-ABA is expected to be limited as a result of the ready degradation of S-ABA and the limited time of application.

MRID 474705-14, *An Acute Toxicity Study with the Earthworm in an Artificial Soil Substrate.*

This is non-guideline study conducted in compliance with GLP standards to assess the acute effects of S-ABA on earthworms for 14 days in artificial soil substrate. The test substance was VBC-30054, (97.0%) S-ABA TGAI. Test animals were earthworms, *Eisenia fetida,* obtained from University of Maryland, Queenstown, MD. Ninety adult worms were exposed to a single dose of 1000 mg/kg of ABA in soil, and negative control groups. Four replicates chambers per treatment contained 10 earthworm per chamber. Observations of mortality and clinical signs were observed daily.
Handling of test organism, preparation of soil substratum and physical properties of test soil, description of test chambers, and environmental conditions were reported. The study was conducted according to procedures outlined in OECD Guidelines No. 207.
A reference toxicity test, exposing worms to 13, 25, and 50 mg a.i. chloroacetamide/kg dry soil, was conducted under a separate protocol and similar testing conditions, using earthworms from the same source. Body weights were statistically compared by Dunnett's 1-tailed test of means (Alpha =0.05). Data was tested for normality and homogeneity of variance. LD50 and NOEL was determined by visual inspection of mortality and clinical signs. No mortality was observed. All worms were normal. The LD50 was < 50%, and the LC50 > 1000 mg/kg in dry soil.

Deficiency: Homogeneity and stability of test substance in the soil were not determined throughout the study.

474705-15, *Environmental Safety Assessment of Natural Abscisic Acid (Zhu, et al. (2000)).*

The study provides supplemental information on non-target birds, Japanese quail (*Coturnix coturnix japonica*), and insects, feeding and contact toxicity of S-ABA to Italian worker bees.

Purity of the test substance was 90%, and LD50 > 180 mg/quail. Avian LD50 values are most frequently seen reported as mg active constituent/kg of bird body weight. Assuming the quail treated had body-weights that were not substantially different from the initial 100 g, the available LD50 dose of >180 mg S-ABA/quail are equivalent to >180 mg S-ABA/100 g quail body weight or >1800 mg/kg body weight.

Test organism: Zebra fish (*Brachydanio rerio*), with the average body length of 2.3 cm and body weight of 0.15 grams. Fish were held in a tank for one week until the death rate was less than 5%. Pre-tests were conducted to determine the minimum concentration of S-ABA for fish to completely die and the maximum concentration of S-ABA for fish to completely survive. Seven concentrations were set up within the concentration range determined by 1.2 times the deferential geometric rule. These concentrations of chemical were 2000, 1666, 1388, 1157, 964, 804, and 0 mg/L (it was not identified in the report whether this value refers to the nominal concentration or the nominal concentration corrected for the 90% purity of the S-ABA used). For each treatment, ten liters of chemical solution were used. Ten zebra fish were placed in each fish tank. The toxic symptoms and death rate were observed at 24, 48, 72, and 96 hours after treatment.

Test results at 24, 48, 72 and 96 hours, repectively.

LC50	>2000	1758	1465	1312
95% Confidence limits	Not reported	1730-1786	1314-1632	1138-1500
Primary reviewer determined LC50 values (95% fiducial limits)	>2000	1899 (1636-2807)	1496 (1317-1780)	1311 (1152-1503)

Zebra fish in each treatment had un-adaptive (i.e. adverse) reactions to S-ABA at the beginning of the experiment, i.e. fish swam rapidly and breathed at water surface. Fish treated with S-ABA above 1157 mg/L were most sensitive. These phenomena disappeared after several hours. Fishes began to die at 48 hours after treatment. For fish treated with 2000 mg/L there was 100% mortality at 96 h after treatment. The LC50 values for Zebra fish at 48 hours was 1758 mg/L, at 72 hours was 1465 mg/L and at 96 hours was 1312 mg/L

The primary reviewer adjusted the following endpoints based on 90% purity of the test substance:

LC50: 96 h = 1180 mg/L; 72 h = 1318 mg/L; 48 h= 1582 mg/L; 24 h>1800 mg/L

Test Organism: Italian worker bee. Test Methods: Feeding toxicity – Thirty bees were raised in small cages made from wood, with the size of 10 cm x 10 cm x 5 cm. Two sides of the cage were covered with cheesecloth. The chemical solution was prepared as 1:1 honey:solution mixture. The prepared chemical solution was added to 10 mL beaker filled with cotton. Beaker was placed upside down on the top of the cage on a side covered with cheesecloth. S-ABA concentrations were; 500, 100, 25, 5, and 0 mg/L.

Contact Toxicity – S-ABA (90% purity) was prepared at five different concentrations, 5000,

3300, 2200, 1481, 987, and 0 mg/L. Ten bees were in each treatment group. A 2 µL portion of each solution was dropped to the chest deep backplane of the bee with a micropipette. Bees in each treatment group were treated with 10, 6.6, 4.4, 3.0, 2.0, and 0.0 µg of S-ABA/bee. Bees were put back into the cage and kept as usual. Toxicity symptoms and mortality were observed at 24, 48, 72, and 96 hours after treatment. Results indicated that there were no significant toxic symptoms in each treatment group of bees. Death numbers was also low. A 30% mortality was seen only in the high dose group. The LD50 at 96 hours was >10 µg/bee. ABA is classified as low toxicity to bees (based on the Chinese government's classification that pesticides with an LD50 > 10 µg/bee are of low bee toxicity).

3. Environmental Fate

474704-13, *Evaluation of the Environmental Safety of S-Abscisic acid (Shi, L. (2004)).*

The objective of this report was to summarize physical chemistry data and environmental toxicity potential of S-abscisic acid (S-ABA). S-ABA was tested for characteristics of hydrolysis, photolysis and degradation in the soil. However, results are inconclusive because information on whether the solutions were protected from visible or UV light during the hydrolysis study was not specifically located in the report; the degradation data presented showed degradation between 32 and 45% of the initial S-ABA, and the degradation products were not identified. Absence of information on whether degradation products were isolated and identified constitutes a significant deficiency in this study.

Results from the recovery of S-abscisic acid (S-ABA) from soil determinations (based on Table 4-1, Shi (2004).

Soil concentration, mg S-abscisic acid/kg soil	Measured S-ABA concentration (three replicates)	Percentage recovery (%)	Average recovery (%)	RSD*
0.05	0.044 0.046 0.042	88.0 (88.0) 95.6 (92.0) 84.5 (84.0)	88.4 (88.0)	4.55 (4.55)
0.10	0.089 0.101 0.092	88.8 (89.0) 101 (101.0) 91.5 (92.0)	93.6 (94.0)	6.62 (6.64)
1.00	0.840 0.936 0.991	84.0 (84.0) 93.6 (93.6) 99.1 (99.1)	92.2 (92.2)	8.24 (8.29)

* RSD = Relative standard deviation = (standard deviation/mean) X 100. Reviewer determined (Microsoft Excel) values (in brackets) are based on the data presented in the study report.

- Details on the properties of the soil used were not provided. Apart from recalculation of the percentage and average recoveries and the relative standard deviation, the summary report did not provide sufficient data for any further validation of the method.

- No methods of analysis for determination of S-ABA in sediment were provided.

Hydrolysis of S-abscisic acid at various pH and temperature values.

	S-ABA concentrations, (nominal time zero value of 1.0)					
Time (days)	25° C			50° C		
	pH 5.0	pH 7.0	pH 9.0	pH 5.0	pH 7.0	pH 9.0
0	0.980	0.986	0.986	0.966	1.04	1.03
5	----	----	----	0.922	0.906	0.989
9	0.979	0.914	0.914	0.912	0.884	0.945
14	0.936	0.900	0.889	0.894	0.870	0.898
24	0.854	0.856	0.864	0.820	0.827	0.858
36	0.764	0.816	0.742	0.767	0.726	0.721
48	0.715	0.738	0.674	0.706	0.656	0.683
72	0.624	0.657	0.669	0.608	0.580	0.641
% Hydrolysis*	36.3%	33.4%	32.3%	37.0%	44.2%	35.2%
% Hydrolysis reported by Schick (2008d)	pH 4 2.8% over 32 days	Not determined	Not determined	pH 4 12.9% over 32 days at 40°C	<3% over 5 days	<3% over 5 days
T1/2 (days)	100	126	116	108	91.2	97.6
r=	-0.990	-0.996	-0.953	-0.998	-0.982	-0.971

* % hydrolysis at 72 days; T1/2 (days) = half-life in days with n = 7 in all cases.
Note: all percentage hydrolysis at 72 days and calculated half-lives were recalculated by the reviewer using Microsoft Excel and the data provided and confirmed as correctly determined.

The report indicates that the buffer solutions and the containers used were sterilised (high temperature, high pressure) and the pHs of the sterilised buffer solutions were recalibrated, Information on whether the solutions were protected from visible or UV light during the hydrolysis study was not specifically located in the report.
The degradation data presented showed that between 32 and 45% of the initial S-ABA was degraded. The report has not addressed what the degradates were – OECD TG 111 (Hydrolysis as a Function of pH) states that any major hydrolysis products (at least those representing > 10% of the applied dose) should be identified by appropriate analytical methods. The absence of information on whether degradates were isolated and determined is a significant deficiency in this case.
Experimental results from the photolysis of S-abscisic acid in water solution under artificial sunlight conditions (Shi, 2004).

Illuminating time (minutes)	S-abscisic acid concentration, mg/L
0.0	1.95
15	1.20

30	1.03
45	0.69
50	0.47
90	0.51
120	0.27
150	0.22
210	0.10

The relationship between concentrations of S-abscisic acid and time was reported as: Ln C = 0.380 – 0.0132t or C = 1.46e-0.0132t (photolysis rate constant = 0.0132 min-1.)

The reported half-life, t1/2, was 52.5 minutes (n = 9 and r = 0.980 with R2 = 0.9606)

The reviewer determined values using Microsoft Excel and the above (mean) data gave a t1/2 = 53.3 minutes (R2 = 0.9453, r = 0.972).

Assuming first-order kinetics, the aquatic half-life under the tested photolysis conditions was 52.5 minutes. Based on [Chinese] grading standards, S-abscisic acid was rated as an easily photolysable pesticide (half-life less than 3 hours). According to the Mensink et al. (1995) classification, S-abscisic acid is classed as very readily degraded by phototransformation in water (half-life less than 1 day).

While the summary report provides clear evidence of the instability of S-ABA to light, there a number of uncertainties associated with the study. These are:

- The lack of information as to whether the study was conducted according to OECD or OPPTS guidelines;
- The uncertainty as to the actual intensity of the ultraviolet light used;
- Lack of certainty with respect to the use of a filtered Xenon lamp; and
- The lack of identification of the degradation products formed.

The photoisomerization and photodegradation of ABA have been addressed a number of times in the published literature over the last 30 years. Published data indicate that photoisomerization (using ultraviolet irradiation) will occur readily and quickly. The methyl ester of cis-, trans-ABA is converted to a near 50:50 mixture with the trans-, trans-isomer, reaching equilibrium within about six hours (Lenton et al., 1971).

When abscisic acid (cis-trans understood) was irradiated with UV light at 254 nm for 120 minutes, multiple degradation products formed (including the trans-trans isomer plus at least three other degradation products). Photolysis at 254 nm resulted in rapid isomerisation (cis/trans to trans/trans) and further photolysis, i.e. degradation of the S-ABA or its photoisomers. In contrast, photolysis at sunlight wavelengths results essentially in the cis/trans and trans/trans

interconversion. Consequently, the conclusion is drawn that S-ABA in natural waters can be expected to undergo photoisomerisation to form an approximately 50:50 mixture of cis/trans and trans/trans isomers. Optimum wavelength for photoisomerisation appeared to be in the UV-A range (320-400 nm). It was also noted that any study which measured only the decrease in an optical isomer of abscisic acid would not be able to differentiate between photolysis and isomerisation.

Endangered Species Assessment

No effect determination is based on the low toxicity of S-ABA and lack of adverse toxicological effects of S-ABA (TGAI) on non-target terrestrial and aquatic organisms tested. However, effects on non-target plants can not be disregarded in line with S-abscisic acid function as a plant hormone.

REFERENCES

cc: *Clara Fuentes*, *Russell Jones*, Chris Pfeifer BPPD Chron File, IHAD/ARS
, FT, PY-S: *Dec. 10, 2009.*

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

DEC 02 2009

OFFICE OF PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

DATE: Dec. 2, 2009.

SUBJECT: Science Review in Support of the Registration of VBC 30054, containing 99.3 % w/w enantiomer S-Abscisic acid, Technical Grade Active Ingredient (TGAI).

Decision Number: 397560
DP Number: 355133
EPA File Symbol Number: 73049-UAN
Chemical Class: Biochemical
PC Code: 272000
CAS Number: 21293-29-8
Active Ingredient Tolerance Exemptions:
MRID Numbers: 474704-01, 474704-03, 474704-06, 474704-10, 474704-11, 474704-12.

FROM: Clara Fuentes, Ph.D. Entomologist
Biochemical Pesticides Branch
Biopesticides & Pollution Prevention Division (7511P)

THROUGH : Russell Jones, Ph.D. Senior Scientist.
Biochemical Pesticides Branch
Biopesticides & Pollution Prevention Division (7511P)

TO: Chris Pfeifer, Regulatory Action Leader
Biochemical Pesticides Branch
Biopesticides & Pollution Prevention Division (7511P)

ACTION REQUESTED

Valent Biosciences requests registration of 99.3 % w/w enantiomer S-Abscisic acid, Technical Grade Active Ingredient (TGAI), which is a plant growth regulator (PGR) intended for use as manufacturing use product (MP) for formulation of end use products. In support of this registration, the registrant has submitted product chemistry data in MRIDs 474704-01, 474704-03, 474704-06, 474704-10, 474704-11, 474704-12. This is U.S.EPA secondary review in conjunction with Pesticides Programs, APVMA, Australia.

RECOMMENDATIONS AND CONCLUSIONS

Product chemistry data are unacceptable. The following deficiencies have been identified and they need to be resolved to make the data acceptable for registration of EPA Reg. No. 73049-UAN.

Deficiency # 1: The registrant needs to address Storage stability (OPPTS 830.6317) and Corrosion characteristics (OPPTS 830.6320) for the proposed manufacturing product to satisfy product chemistry data requirements under U.S. Code of Federal Regulation, 40 CFR §158.310. (Physical/Chemical Characteristics are listed in Table 1).

Deficiency #2: Specifications of S-abscisic acid were generated from a single batch, and from five batch analyses. The registrant should clarify which is the specification that applies to the technical S-abscisic acid proposed for registration. (Tables 2 and 3 refer to S-ABA specifications).

Deficiency # 3: The registrant is requested to provide some analyses of batches of the technical active ingredient to confirm its optical purity i.e. the proportions of the S and R enantiomers. The HPLC methods for determination of purity of the active ingredient do not provide any confirmation of the stereochemistry of abscisic acid, as the methods do not use a chiral column to separate the two enantiomers. The measurement of the specific optical rotation of S-abscisic acid is acknowledged, however this measurement only appears to have been conducted for a batch of the material used as a reference standard (99.7% purity). The registrant is asked to conduct the batch analysis on the technical material proposed for registration. (Tabulated data for five batch, and one batch analyses are presented in tables 4 and 5, respectively).

Deficiency #4: The registrant should explain different impurity profiles for the five batches tested by PTRL West, and single batch tested by Lomon in tables 4 and 5, respectively.

Deficiency # 5: The registrant should clarify the interpretation of the findings for determination of structurally related impurities of the active ingredient. According to the sample chromatograms for [redacted]

Deficiency # 6: The registrant should provide more details on validation data for the batch analysis conducted by Lomon Biotechnology. (Key instrumental parameters of Lomon method for determination of S-abscisic acid are tabulated in Table 8). Related impurities, [redacted] They were

quantified using the same HPLC-UV method. Representative chromatograms and spectra were supplied, although validation data was not.

Deficiency # 7: The registrant should explain the origin of the higher mass peaks at 331.3, 527.7, 549.5, 617.6, 813.8, 835.9 and 903.7 detected in spectroscopic analysis of S-Abscisic acid. The mass spectrum showed a strong molecular ion peak at m/z = 263.2. Fragment ion peaks at m/z = 219.3 and 153.0 were due to elimination of a CO_2 fragment and loss of the entire pentadienoic acid side chain respectively. However, the origin of the higher mass peaks is not clear.

(Spectral assignment of ^{1}H and ^{13}C NMR resonances data are tabulated in Table 9).

Deficiency # 8: The applicant should clarify whether an analysis of the content of S-abscisic acid of the reference standard was conducted using a primary analytical method. HPLC analysis of the purity of the active ingredient was conducted using an isocratic reverse phase HPLC-UV (262 nm) method that was similar to those used for the analyses in other physico-chemical property studies (e.g. water solubility, storage stability, vapour pressure). Total impurities detected by HPLC were [redacted] The purity of the material was calculated as 99.7% by subtraction of the total HPLC impurities and residue on ignition. However, the analytical method for determination S-ABA content in the reference standard is not addressed, and it should be.

STUDY SUMMARIES

Product Chemistry

S-Absisic acid is an essentially non-volatile white odourless solid, slightly soluble in water, highly soluble in polar organic solvents, slightly soluble in aromatic non-polar organic solvents and essentially insoluble in aliphatic non-polar solvents. It has a $\log_{10}P_{OW}$ value of 1.8 and 0.94 in the unionised and ionised forms respectively and as a result is not likely to be fat soluble or to bio-accumulate. It decomposes with melting at 159.2-162.2 °C. As its name suggests, it is a weak acid with a pK_a of 4.61. No hydrolysis was observed in preliminary experiments over 5 days at 50 °C at pH 7 and 9. Very slow hydrolysis (half life > 2 years) was observed in pH 4 buffer at 25 °C, with more rapid degradation (half life of 162 days) in pH 4 buffer at 40 °C. *S*-Abscisic acid demonstrates excellent safety properties, as it is not highly flammable, is not heat, friction or shock sensitive and does not undergo self-ignition. It is stable under accelerated storage conditions (14 days at 54 °C), with or without the presence of metals (aluminium or iron shot) or metal ions (aluminium acetate or iron(II) acetate). It is not reduced by zinc metal, but is oxidised by potassium permanganate (a 5% solution). Manganese dioxide is formed as a by-product.

(Manufacturing process is described in the Confidential Appendix).

Table 1. Physico-chemical properties of *S*-abscisic acid

Property	Value	Method reference
Melting point	Did not melt, decomposes	EEC method A.1 and A.2

Property	Value	Method reference
Temperature of decomposition	159.2-162.2 °C (99.7% purity, 96.2% purity)	EEC method A.1 and A.2
Appearance and odour	White odorless powder (25 °C, 99.7% purity)	OPPTS Guidelines 830.630, 830.6302, and 830.6304.
Density	1.21 g/cm^3 (96.2% purity)	OPPTS Guideline No. 830.7300.
Vapor pressure	<2 x 10^{-6} Pa (25 °C, 99.7% purity active) 5.8 x 10^{-7} Pa (calculated)	OPPTS Guideline No. 830.7950.
Henry's Law constant	4.8 x 10^{-8} Pa m^3/mol	Calculation from vapour pressure and water solubility.
Water solubility (99.7% purity active, 20 °C)	Distilled water: 3192 mg/L pH 4 buffer: 3102 mg/L	Shake flask method.
Solubility in organic solvents (99.7% purity active, 20 °C)	Methanol: 506.8 g/L Acetone: 290.2 g/L Ethyl acetate: 92.175 g/L 1,2-Dichloroethane: 10.95 g/L Xylene: 0.265 g/L Octanol: 54.8 g/L n-Heptane: 0.0057 g/L	OECD Guideline 105/OPPTS Guideline No. 830.7840
Octanol/water partition coefficient (99.7% purity active)	$\log_{10}P_{OW}$ (unionised form) = 1.8 $\log_{10}P_{OW}$ (unionised form) = 0.94	OPPTS Guideline No. 830.7570.
Hydrolysis (99.7% purity active,)	pH 4: k (25 °C) = -0.00088 days^{-1} (half life 792 days) pH 4: k (40 °C) = -0.0043 days^{-1} (half life 162 days) pH 7: very slow hydrolysis pH 9: very slow hydrolysis	OECD Guideline No. 111 and OPPTS Guideline No. 835.2110.
Dissociation constant	pK_a = 4.61 (99.7% purity active)	Titration with 0.1M NaOH
pH of solution	3.32 (1% aqueous solution/suspension of 96.2% purity active)	OPPTS Guideline No. 830.7000.
Specific rotation	409.97° (in ethanol, 10.1 mg/mL, 20 °C)	
Flammability	Not highly flammable (97.0% purity active)	EEC method A10
Explosive properties	Not heat, friction or shock sensitive (97.0% purity active)	EEC method A14
Self-ignition temperature	No self heating below 400 °C (97.0% purity active)	EEC method A16
Accelerated storage stability	No significant degradation on storage at 54 °C for 14 days (97.0% purity active)	OPPTS Guideline No. 830.6313
Oxidative/reductive stability	Oxidised by 5% potassium permanganate solution, which was converted to manganese dioxide. No changes observed with zinc metal, carbon dioxide or water. (97.0% purity active)	OPPTS Guideline No. 830.6314
Stability in the presence of metals and metal ions	No significant degradation over 14 days at 54 °C when stored in the presence of aluminium shot, iron shot, aluminium acetate or iron(II) acetate. (97.0% purity active)	OPPTS Guideline No. 830.6313

The physico-chemical properties were determined using suitable test methods, in accordance with the OECD Principles of Good Laboratory Practice (GLP).

S-Abscisic acid specifications

Table 2: Specification set 1

[redacted]

Table 3: Specification set 2

[redacted]

Analytical methods for analysis of the active ingredient.

a) Brief method details

A reverse-phase isocratic HPLC-UV method was employed to quantify the *S*-abscisic acid content of the technical active ingredient. Quantification was achieved by linear regression external standard calibration (99.7% purity reference standard). Sample raw data allowed calculations to be reproduced.

b) Conclusion

The analytical method has been appropriately validated for analysis of *S*-abscisic acid, demonstrates excellent linearity, precision and accuracy and shows no evidence of any co-eluting interferents. It is therefore suitable for the determination of the purity of technical *S*-abscisic acid.

Batch analysis of technical *S*-abscisic acid

PTRL West Inc analyzed five batches of technical *S*-abscisic acid for active content and levels of impurities. The results are tabulated below:

Recommendation of Division Directors Negotiated Due Dates		
Decision#: 397560	**Registration#: 73049-UAN**	**Petition #: 8F7391**
Fee Category: B590	**PRIA Decision Time Frame: 16 Months**	
Submitted by: Chris Pfeifer	**Branch: BPB**	**Date: 11/23/9**
Company: Valent Biosciences Corporation		
Original Due Date: 11/29/9	**Proposed New Due Date: 3/1/10**	
Previous Negotiated Due Dates: NA		
Is the "Fix" in-house? NA	**If not, date "Fix" expected: NA**	

Issue (describe in detail): EPA is engaged in a joint review with Australia (APVMA). As part of this review, EPA and APVMA agreed on data requirements and assigned primary and secondary review responsibilities. In the process of Australia's review, they uncovered some issues with their ecotoxicity submission, which required redress from the registrant. As a result, Australia's primary review for ecotoxicity was delayed (by approximately 5 months). Australia informed EPA of potential delays in May and again in July.

Summary of Deficiency Type(s): **Not Submitted (N)** **Deficiencies (D)**
Product Chemistry: ___ **Acute Tox:** ___ **Efficacy:** ___ **Labeling:** ____ **Other?:** **Risk Assessment**

Describe Interactions with Company (describe when contacted and company's response including response to previous negotiated due dates): EPA has kept regular communications with both APMVA and the registrant. EPA first learned of the delays in Australia from the registrant in May of 2009 with regard to the status of the Australian reviews. The registrant informed EPA of further delay by email on 7/10/9 and 7/21/9. EPA communicated continued review delays to the registrant by phone in September, by phone in October, and in person on a November 5, 2009 BPIA meeting.

"75 Day" Letter sent? ___ **(Date sent)** **__X__ No and reason for none**? In this case, a deficiency is only practicable, if the information received is inadequate; and we won't know until receipt of that information. Given what we know from past reviews of this active ingredient, we do not anticipate any issues.

Rationale for Proposed Due Date: Rationale for Proposed Due Date: This renegotiation request is for an extension which could allow for completion of this B590 action by 3/1/10, provided that Australia's reviews do not reveal any deficiencies. Because of the unique nature of this joint review with Australia – APVMA's timelines and administrative processes –delays were incurred. Because the registrant has attempted to respond in good faith to the requirements of international registration, and because the registrant had not realized that they had altered Australia's review timeline, the registrant and BPPD's regulatory staff have agreed to attempt to expedite the balance of this review. The registrant and BPPD's regulatory staff believe that an additional 3 months should be enough for completion of the risk assessment and to allow for the public participation process. This extension makes for a renegotiated PRIA date of 3/1/10. Confirmation of the agreement can be found in the attached email.

Registrant notified that this is the last negotiation? ____ **Yes** **__√__ Not Applicable**

Approve:	**Disapprove:**

If disapproved, action to be taken:

OD or DOD Signature:	**Date:**
	11/25/09

Revised May 2007

Recommendation of Division Directors Negotiated Due Dates		
Decision#: 397560	**Registration#: 73049-UAN**	**Petition #: 8F7391**
Fee Category: B590	**PRIA Decision Time Frame: 16 Months**	
Submitted by: Chris Pfeifer	**Branch: BPB**	**Date: 11/23/9**
Company: Valent Biosciences Corporation		
Original Due Date: 11/29/9	**Proposed New Due Date: 3/1/10**	
Previous Negotiated Due Dates: NA		
Is the "Fix" in-house? NA	**If not, date "Fix" expected: NA**	

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Registrant notified that this is the last negotiation? ____ **Yes** __√__ **Not Applicable**

Approve:	**Disapprove:**
X	

If disapproved, action to be taken:

OD or DOD Signature:	**Date:**
	11/25/09

Revised May 2007

S-ABA Registration PRIA Timeline extension
Bade, Thomas
to:
Linda Hollis, Chris Pfeifer
11/25/2009 11:23 AM
Cc:
"Herrero, Maria"
Show Details

Regarding the phone message from EPA received on November 17th (4:17 pm) 'renegotiation of the PRIA deadline for the S-Abscisic acid (S-ABA) TGAI and end use products registrations';

[OPP Decision Number: D-397561, File Symbol 8F7391 receipt date: 09-July-2008,
OPP Decision Number: D-397560, File Symbol 73049-UAN receipt date: 08-July-2008,
OPP Decision Number: D-397562, File Symbol 73049-UAR receipt date: 08-July-2008,
OPP Decision Number: D-397563, File Symbol 73049-UAE receipt date: 08-July-2008],

VBC understands there has been difficulty in the efficient coordination of the Joint Review process between APVMA and EPA. Valent BioSciences (VBC) agrees to the extension of these PRIA deadlines from the original PRIA date of November 29, 2009 to March 1, 2010.

EPA Primary Reviewer: Clara Fuentes, Ph.D., Entomologist

Date: Nov. 17, 2009

Data Evaluation Record

NOV 17 2009

STUDY TYPES: VBC-30054 Preliminary Developmental Toxicity in Rats.

DP BARCODE: 355254

P.C. CODE: 129028 (E,E-8,10-dodecadien-1-ol)

DECISION NO.: 397560

REGISTRATION NO: 73049-UAN

PRODUCT NAME: S-ABSCISIC ACID (S-ABA) TGAI

MRID NO. 474705-11

SPONSOR: Valent Biossciences Corporation
870 Technology Way, Suite 100
Libertyville, IL 60048 USA.

TEST FACILITY: Charles River laboratories
Tranent, Edinburgh EH33 2NE, UK

STUDY SUMMARY:

The purpose of this study was to estimate the maximum tolerable dose of VBC-30054 in the diet of pregnant females and their fetuses. The test animal was the rat because it is a standard rodent species representative of mammals, and required by regulatory authorities in the United Kingdom, where the study was conducted. The dietary route was chosen for administration of the test substance because this is the likely route of exposure in man.

Diet formulations were prepared in one occasion by mixing required amounts of VBC-30054 with required amounts of blank diet for 20 minutes, sealed and refrigerated. They were analyzed for homogeneity in triplicate samples of 50 g. immediately following preparation. The blank diet

was supplied with an analytical certificate of nutritive constituents and contaminants. Analysis of dosing formulations showed a low coefficient of variation (< 1.5%), indicating that the formulations were homogenous.

Mated female Sprague-Dawley rats were randomly assigned to 3 treatment groups, including control. Each treatment consisted of dose levels of 0, 10000, and 20000 p.p.m. of VBC-30054 Technical. Each treatment group contained an equal number of 6 pregnant females. The animals were continually dosed orally via their diets from day 6 to day 20 of gestation period. Day 6 of gestation was considered day of implantation, occurring 6 days after day of mating.

There were no clinical signs or necropsy findings at doses up to 20000 p.p.m. At doses 10000 and 20000 p.pm., there was slight reduction in body weight gains over Days 17-20 of gestation; it was not clear that these weight reductions were related to treatments. Slight intergroup differences in pregnancy and fetal weights were too small to be treatment related. The dose levels up to 20000 p.p.m of VBC-30054 show no developmental toxicity effects in rats.

The rats were 9 weeks of age when mated. No more than one female was mated by any one male. All animal were examined prior to testing and found healthy.

Rearing conditions were within acceptable range, except for humidity which was 26 to 57 % instead of the target range 55 ±15 % on seven occasions. Study results were considered not to be affected by these deviations. Rats were housed in individual cages made of polypropylene (42 x 27 x 20 cm). Water was provided *ad libitum*, and analyzed for dissolved materials. Water and bedding, made of sterilized wood shavings, were provided and changed regularly.

Animals were observed for viability twice a day, early morning and late evening, and examined for any reactions to treatments. Body weights were recorded on days 4, 6, 9, 13, 17 and 20 of gestation. The achieved intake of S-ABA was calculated using the following formula:

Achieved Intake = (Mean Food Consumption x Dietary nominal Concentration) / Mean Body Weight.

All animals were killed on day 20 and examined for necropsy, number of corpora lutea graviditatis per ovary, and number and position of implantation sites in the uterus. Each fetus was weighed and examined for external visible abnormalities.

There were no clinical observations or necropsy attributable to treatments. Slight intergroup differences in group mean food consumption were too small to be attributed to treatment effects. The values for achieved dose intake were generally proportional to the dietary concentrations. At doses 10000 and 20000 p.p.m., there was slight reduction in body weight over days 17 to 20 of gestation, compared to controls. It is not clear if this effect was due to treatments.

At 20000 p.p.m., pregnancy performance was comparable to control. At 10000 p.p.m., the slight increase in early embryonic deaths was mainly due to one animal, assuming that this early death was incidental. Intergroup differences in fetal weights were too small to be attributable to treatments.

No formal statistical analysis was performed because it was not considered necessary.

Based on these results, it is concluded that dose level up to 20000 p.p.m. in food do not show adverse effects of developmental toxicity in rats.

REVIEWER COMMENTS:

The study is acceptable. However, it would have been better if the researcher had performed statistical analysis to conclusively confirm that slight reduction in body weight, and other observations are not statistically significant and therefore, not due to treatment effects.

EPA Primary Reviewer: Clara Fuentes, Ph.D., Entomologist

Date: Nov. 17, 2009

Data Evaluation Record

NOV 17 2009

STUDY TYPES: VBC-30054 One Week Dose Range Finding Study in Rats with Dermal Administration

DP BARCODE: 355254

P.C. CODE: 129028 (E,E-8,10-dodecadien-1-ol)

DECISION NO.: 397560

REGISTRATION NO: 73049-UAN

PRODUCT NAME: S-ABSCISIC ACID (S-ABA) TGAI

MRID NO. 474705-07

SPONSOR: Valent Biossciences Corporation
870 Technology Way, Suite 100
Libertyville, IL 60048 USA.

TEST FACILITY: Charles River laboratories
Tranent, Edinburgh EH33 2NE, UK

STUDY SUMMARY:

The objective of the study was to assess the dermal toxicity of VBC-30054 (TGAI) on rats exposed continuously to increasing S-ABA doses for one week. Four groups of 5 male and 5 female Sprague-Dawley rats were assigned to dose treatments of 0, 10, 100, and 1000 mg/kg/day of test material VBC-30054 mixed with 0.5% high viscosity carboxymethyl cellulose. The treatments were applied evenly over an area approximately 6 x 6 cm of exposed skin, and left in place for 6 hours. Applications were repeated daily. The experiment lasted 1 week. All animal were killed after one week of treatment. Ten major organs were weighed and fixed in 10% neutral buffered formalin with the exception of the testes which were fixed in Bouins fluid. Implants were retained to be identified. Isolated incidents of desquamation and well defined erythema were observed in groups receiving less than 1000 mg/kg/day dose. These findings

were not associated to toxicity. There were no treatment related clinical signs. Slight differences in body and organ weights were not significantly different from controls; adrenal gland weights in animals receiving the highest dose, and ovarian weights in females receiving 100 and 1000 mg/kg/day were slightly lower than controls and not significantly different. There were no necropsy findings that were considered to be related to treatments. In conclusion, the No Adverse Effect Level (NOAEL) is 1000 mg/kg/day

Reviewer Comments:

The main difference in males body weight is seen between group treated with 100 mg/kg/day and group treated with 1000 mg/kg/day starting on day 4th of treatment. Among females, the biggest difference was between controls and those treated with the lowest dose, 10 mg/kg/day.

There is little explanation for the information presented on tables and graphs, and no discussion on statistical procedures for analysis and interpretation of results.

Data should be analyzed as a 4 x 2 factorial for dose levels by gender to determine whether there is a significant interaction between dose and genders.

EPA Primary Reviewer: Clara Fuentes, Ph.D., Entomologist

Date: Nov. 17, 2009

Data Evaluation Record

NOV 1 7 2009

STUDY TYPES: VBC-30054: 3 Week Toxicity Study in Rats with Dermal Administration

DP BARCODE: 355254

P.C. CODE: 129028 (E,E-8,10-dodecadien-1-ol)

DECISION NO.: 397560

REGISTRATION NO: 73049-UAN

PRODUCT NAME: S-ABSCISIC ACID (S-ABA) TGAI

MRID NO. 474705-08

SPONSOR: Valent Biossciences Corporation
870 Technology Way, Suite 100
Libertyville, IL 60048 USA.

TEST FACILITY: Charles River Laboratories
Tranent, Edinburgh,
EH33 2NE
UK

STUDY SUMMARY

The objective of the study is to evaluate the mammalian toxicity of VBC-30054 Technical Grade Active Ingredient (TGAI) after continuous daily exposure of 6 hours for 21 days in rats. The study was designed to be in accordance with OPPTS 870.3200 guidance and OECD Guidelines No. 410.

Four groups of 5 male and female Sprage Dawley rats, approximately 7 weeks old, weighing 221-269 g. (males), and 168- 205 g. (females), were randomly assigned to 4 dose treatments (0, 100, 300 and 1000 mg/kg/day of VCB-30054). The animals were received in the laboratory when they were approximately 5 weeks old, and allowed to acclimate for 2 weeks before initiation of the test. The study consisted of 4 completely randomized treatments. Each treatment consisted of increasing doses of VCB-30054 at 0, 100, 300 and 1000 mg/kg/day, applied daily via the dermal route to 5 male and female rats per treatment for a period of 3 weeks. The test material was properly identified and stored. Formulations were prepared daily by mixing appropriate amounts of test material with 0.5% high viscosity carboxymethylcellulose. Concentrations of 0, 50, 150 and 500 mg/ml were examined for stability and homogeneity before being applied to a 2 mL/kg volume to concentration levels of 0, 100, 300 and 1000 mg/kg, respectively. Each testing dose formulation was sampled in triplicates and analyzed for homogeneity and accuracy. Nominal concentrations for testing doses were within acceptable ranges (around ± 5 %), except for the intermediate dose formulation that was -12 % from nominal on day 1 of treatment.

The animals were housed individually by sex and dose treatment group in suspended polycarbonate cages (42 x 27 x 20 cm) with stainless steel grid tops and bottoms. Water and food were supplied *ad libitum,* except during urine collection. Urine samples were collected from all animals during 3 week period by placing the animals into metabolic cages. Urine samples were collected over 4 hours period. During this time, animals were deprived of food and water.

The diet was supplied with a batch analysis for nutrient components and contaminant. Water was also regularly analyzed for dissolved materials, and found acceptable. Rearing conditions in the laboratory were maintained within target ranges throughout the test. Temperature was 19 ° C to 23 ° C, and RH was 40 – 70 %. Photoperiod was 7 to 19 hours cycle.

The lumbar region of the animals was clipped to expose the skin (approximately 6 x 6 cm) with the test formulation being spread evenly over this area. A dressing of foil gauze and self adhesive bandage was wrapped around the torso to prevent oral ingestion. Following 6 hours of exposure the dressings were removed and the dose area wiped clean with a cloth dampened with distilled water.

All animals were monitored twice a day for viability, skin condition, good health, body weight, or reaction to treatments before application of the test material, and after 6 hours of daily exposure. Food consumption was recorded twice weekly. Ophthalmoscopy was assessed on all animals in control and high dose groups throughout duration of treatments. All animal were killed at the conclusion of the test, and examined for tissue anomalies.

All males and some females at the highest doses, 300 and 1000 mg/kg/day, showed very slight erythema on the application site. Increased in white blood counts were observed in males at the highest dose, 1000 mg/kg/day, and were considered to be of no toxicological significance. There were no histological findings and thus, the No Observed Adverse Effect Level (NOAEL) is set at 1000 mg/kg/day.

Statistical analysis consisted of 2-sided pairwise comparisons of each dose treatment against control. Level of significance was set at $P \leq 0.05$. Males and females were analyzed separately. The tested endpoints were body weight, food consumption, hematology, clinical chemistry, and urinalysis data. Variance was found homogenous, and ANOVA was used for determination of statistically significant effects due to treatments. Pairwise comparisons were performed only if the overall F-test was significant.

Clinical observations included stained fur, discharge from the eye(s), and skin discoloration in some animals treated at 1000 and 300 mg/kg/day doses. Body weights, ophthalmic findings and food consumption showed no notable differences.

Increased white blood cell counts and related parameters, were statistically significant due to increased lymphocyte and neutrophil counts, specially in males at the highest dose treatment. These values were lower at lower doses sand no dose related trend was observed.

No significant differences were reported for clinical chemistry and urinalysis endpoints. No significant differences were reported for body and organ weights. Necropsy and histology findings were not no statistically significant, and no attributable to treatments.

The slight erythema noticed at the dose site for animals at 1000 mg/kg/day dose treatment, and some animals treated with 300 mg/kg/day dose were considered due to normal irritation and not systemic toxicity. It was concluded that increments in white blood cells and associated parameters with no corroborating histological findings indicated that these changes were no toxicologically significant. In conclusion, the higher dose treatments were associated with very slight erythema for both sexes, and increased white blood cell counts and related parameters in males at the highest dose. These results were attributed to the route of administration rather than to treatments and not considered toxicologically significant.

REVIEWER COMMENTS

The study is acceptable pending clarification of the following observations, which may compromise the validity of test findings:

As stated in the study report, several animals removed their bandage used to cover application of the test material, several times during the 6 hours exposure period. These incidents were considered to be inconsequential because the bandages were replaced during the exposure period after approximately 2 hours. However, the study report also states that the removed bandages were replaced (**when found**) during the exposure period.

This statement [**when found**] seems to indicate that only those bandages that were found were replaced as described. It is not clear why some bandages were not found if each animal was individually caged. There is no explanation concerning those bandages that were not found. Were they replaced with new bandages? Furthermore, if the purpose of the bandage was to prevent ingestion of the test material, and it got replaced within 2 hours period, it is questionable how much of the test material could have been ingested from the exposed skin during that

period. Maybe these incidents are inconsequential; however, their potential for compromising test results can not be ignored or underestimated. This situation is not addressed by the researcher, and it should be.

Several tissues were dissected incorrectly during necropsy evaluation. According to the report, this includes mammary glands from 2 males (animals # 16 and 17) from the highest dose group (refer to section 5.3.4.4, page 23 in study report). Mammary glands are not found in males. If this is a typo, it should be corrected on the study report.

The researcher concludes that following evaluation of the remaining available tissues, these mistakes do not compromise the integrity of results.

Discussion about analytical procedure is adequate. However, the argument made by the research that hematology findings are toxicologically irrelevant because there is no dose dependent trend or dose related response, is questionable. The data was not analyzed for evaluation of trends. Pairwise comparisons of individual treatments against control do not meet that objective. The increase in white blood cell counts and related parameters were statistically significant at the highest dose. Therefore, a statistically significant increase in white blood cell counts at the highest dose tested, 1000 mg/kg/day, indicates a physiological effect due to that treatment. The researcher should provide a more detailed interpretation of such results before concluding that there is no dose related adverse effect.

EPA Primary Reviewer: Clara Fuentes, Ph.D., Entomologist

Date: Nov. 17, 2009

Data Evaluation Record

NOV 17 2009

STUDY TYPES: 4 Week Toxicity Study in Rats with Administration by the Diet

DP BARCODE: 355254

P.C. CODE: 129028 (E,E-8,10-dodecadien-1-ol)

DECISION NO.: 397560

REGISTRATION NO: 73049-UAN

PRODUCT NAME: S-Abscisic acid (S-ABA) TGAI

MRID NO. 474705-09

SPONSOR: Valent Biossciences Corporation
870 Technology Way, Suite 100
Libertyville, IL 60048 USA.

TEST FACILITY: Charles River laboratories
Tranent, Edinburgh EH33 2NE, UK

STUDY SUMMARY:

The objective of this study is to assess the oral toxicity of VBC-30054 (Technical grade S-Abscisic Acid (ABA) administered via oral route for 4 weeks. This study was designed to be compliant with the guidelines of the EU authorities, and is in accordance with the guidelines detailed in the OECD 407 (adopted by the council on 21 September 1998) and OPPTS 870.3050 (July 2000) of the US EPA.

Four groups of 5 male and 5 female Spraque-Dawley rats were dosed continuously by diet for 4 consecutive weeks at levels of 0, 2000, 6000 and 20000 ppm. S-ABA

Diet formulations were prepared by simple mixing of appropriate weighed quantities of test material, S-ABA (TGAI), to measured weights of diet.

Blank diet, without S-ABA, was prepared for control animals.
Diet formulations were prepared weekly, and analyzed in triplicate samples for concentration, homogeneity and stability. The concentrations of the formulations were within ± 5% of the nominal, indicating acceptable accuracy of formulation. The low coefficients of variation indicate satisfactory homogeneity. Concentrations in the diet were constant throughout the treatment period.

Animals were housed 2 or 3 per cage by sex in suspended 59 x 38.5 x 20 cm polypropylene cages with stainless steel grid tops and bottoms containing a separate stainless steel food hopper. Each cage was supplied with a polycarbonate water bottle with a DurethanTM cap and stainless steel nozzle. Beneath each cage was a suspended tray containing absorbent paper. Paper was changed as necessary. Wooden chewsticks were provided to the animals for environmental enrichment. Cages and hoppers were changed once every 2 week. Water bottles were changed at least once each week.

There was automatic control of temperature and humidity. Target ranges were 21°C ± 2°C and RH= 55% ± 15, with a minimum of 15 air changes per hour. It is reported that there were 2 occasions during Week 3 where the humidity was below the target humidity range, but this was considered not to have adversely affected the rats. Light hours were 0700-1900 h. cycle.

Food and water were supplied *at libitum*. Water was analyzed at regular intervals for dissolved materials, heavy metals, pesticide residues, pH, nitrates and nitrites, including bacteriological screening. Food and water were reported not to contain any additional substances at concentration levels to have any influence on the outcome of the study.

Animals were randomly allocated to 4 dose treatment of 0, 2000, 6000 and 20000 ppm. S-ABA The animals were dosed by oral administration for 7 days/week for 4 consecutive weeks. Control animals received blank diet only.

The rats were regularly monitored for any signs of ill health or reaction to treatment throughout the study. Detailed functional observations were performed weekly, with additional functional investigations performed during pretrial and at week 4 of treatment. Body weight and food consumption were recorded at regular intervals until the end of the treatment. Blood and urine samples were collected for laboratory investigations at the end of treatment
On completion of the 4 weeks treatment, all animals receiving 0 and 20000 ppm were subjected to necropsy.

All statistical tests were two-sided and performed at the 5% significance level using in-house software. Males and females were analysed separately. Pairwise comparisons were only performed against the control group (group 1). The following pairwise comparisons were performed:

Control Group vs Low Dose
Control Group vs Intermediate Dose
Control Group vs High Dose

Body weight, hematology, clinical chemistry, selected urinalysis and selected neurotoxicity data were analyzed for homogeneity of variance using the 'F-Max' test. If the group variances appeared homogeneous, a parametric ANOVA was used and pairwise comparisons were made using Fisher's F protected LSD method via Student's test ie pairwise comparisons were made only if the overall F-test is significant. If the variances were heterogeneous, log or square root transformations were used in an attempt to stabilize the variances. If the variances remained heterogeneous, then a Kruskal-Wallis non-parametric ANOVA was used and pairwise comparisons were made using chi squared protection (via z tests, the non-parametric equivalent of Students's t test).

In circumstances where it was not possible to perform the F Max test due to zero standard deviation in at least one group, the non-parametric ANOVA results were reported.
Organ weights were analyzed using ANOVA as above and by analysis of covariance (ANCOVA) using terminal kill body weight as covariate. In addition, organ weights as a percentage of terminal body weight were analyzed using ANOVA as above as an exploratory analysis, but not reported.

In circumstances where the variances in the ANCOVA remained heterogeneous following log or square root transformations or where it was not possible to perform the F-Max test, the untransformed parametric ANCOVA results were reported.
Histological incidence data were analyzed using Fisher's Exact Probability Test.

There were no premature deaths during the study. There were no clinical observations that could be attributed to treatment with VBC-30054.
There were no notable intergroup differences in neurotoxicity clinical observations (Tables 1 and 2, Appendices 7 and 8) in either sex that were attributed to treatments effects.
There were no notable intergroup differences in motor activity (Tables 3-6, Appendices 9-12) in either sex that were considered treatment related.
There were no notable intergroup differences in detailed functional observations (Tables 7-16, Appendices 13-22) in either sex that were attributed to treatment.

After 4 weeks of dose treatments, group mean body weight gain and group mean body weight were slightly lower in males treated at 20000 ppm when compared to controls, but were not statistical significant. Administration of VBC-30054 via the diet for 4 consecutive weeks was associated with slight reductions (without statistical significance) in mean body weight gain in both males and females treated at 20000 ppm only. No notable findings were seen in males and females treated at 2000 and 6000 ppm (Tables 17 and 18, Figures 1 and 2, Appendices 23 and 24).
There was no effect on food consumption (Tables 19 and 20, Appendices, 26 and 27).
There were sporadic incidences where the food consumption in treated groups was higher or lower when compared to their respective controls, however no pattern was established and therefore was not attributed to treatment effect.
There were no findings that could be attributed to treatment of VBC-30054 (Appendix 28).
Mean cell hemoglobin was slightly reduced in males treated at 20000 ppm when compared to controls. Reticulocytes in females were statistically significantly lower in all treated groups however no dose related pattern was seen. White blood cell parameters such as lymphocytes and

neutrophils were slightly lower (without statistical significance) in males treated at 20000 ppm when compared to the controls. Females treated at 20000 ppm had slightly lower lymphocytes without statistical significance when compared to the controls. Neutrophils were statistically significantly lower in all treated female groups when compared to the controls, but this was attributed to two high control values.
Activated partial thromboplastin time was slightly lower in males treated at 20000 ppm with statistically significance.
No notable findings were seen in any other hematological parameters in animals treated at 2000 and 6000 ppm (Tables 21 and 22, Appendices 30 and 31).

Urea was slightly lower in males and females treated at 20000 ppm when compared to their respective controls, but the difference was not statistically significant. Glucose was noted to be statistically significantly lower in males than the controls in a dose related pattern.
No notable findings were seen in any other clinical chemistry parameters (Tables 23 and 24, Appendices 32 and 33).

Specific gravity in males treated at 20000 ppm was slightly lower when compared to the controls, but it was not statistically significant.

Covariant epididymide weights were slightly higher in males treated at 2000 and 6000 ppm in comparison to the controls with statistical significance. Testes weights were slightly higher at 20000 ppm without statistical significance. Males treated at 6000 ppm and above had slightly increased covariant salivary gland weights without statistical significance.
Covariant salivary glands and thyroid glands were slightly increased in females treated at 20000 ppm in comparison to the controls, both without statistical significance. Females treated at 2000 ppm also had higher kidney weights with statistical significance when compared to the controls, however no other notable findings were seen in the other treated groups (Tables 27-30, Appendices 36 and 37).

There were no necropsy findings s at any dose level that were attributed to dose treatments with VBC-30054. All necropsy findings were considered typical of spontaneous arising histological findings in rats of this age and strain (Table 31, Appendix 38).

There were no histological findings at any dose level that were attributed to treatments (Table 32, Appendix 38). All histological findings were considered typical of spontaneous arising histological findings in rats of this age and strain.

The researcher concluded that administration of VBC-30054 via the diet for 4 consecutive weeks was associated with slight reductions (without statistical significance) in mean body weight gain in both males and females treated at 20000 ppm only. There was no effect on food consumption. The slightly lower values without statistical significance of selected white blood cell parameters in males and slightly lower urea in males and females with lower glucose (with statistical significance) in males were only seen in animals treated at 20000 ppm and were not thought to be of toxicological significance due to the lack of any contributing necropsy and histological findings. Very slight effects seen in reticulocytes and white blood cell parameters in all treated

groups were considered to be due to higher than expected control values. Furthermore, there were no neurotoxic findings that were attributed to dose treatments.

In conclusion, under the conditions of this study, the researcher established No Observed Adverse Effect Level (NOAEL) at 20000 ppm.

REVIEWER COMMENTS:

The study is considered acceptable. The study emphasizes neurological endpoints, immunological effects and reproductive organs toxicity as recommended by OPPTS 870.3050 guidelines. The following observation does not constitute a deficiency likely to affect the study results.

There is no description of randomization procedures for allocation of animals to treatments. No detail is provided concerning whether females were nullliparous and nonpregnant. Light cycle was 7:19 h. rather than 12:12 hours, as recommended by OPPTS 870.3100 guidelines.

Dose treatments affected some parameters differently in males and females. Activated partial thromboplastin time was slightly (but statistically significantly) lower in males treated at 20000 ppm. Also, glucose was noted to be statistically significantly lower in treatment than control males in a dose related pattern. Females treated at 2000 ppm had higher kidney weights with statistical significance when compared to controls.

These results indicate a potential interaction between sex and dose levels on the above mentioned parameters. The statistically significant effect of varying doses of S-ABA on these endpoints seems to be mediated by gender because the measured affect is different in males and females. The researcher may analyze these results as a 2 by 4 factorial analysis (4 dose levels by 2 genders) to evaluate a potential interaction between these 2 factors (dose by gender) on thromboplastin parameters, glucose levels, and kidney weights.

EPA Primary Reviewer: Clara Fuentes, Ph.D., Entomologist

Date: Nov. 17, 2009.

Data Evaluation Record

NOV 1 7 2009

STUDY TYPES: 13 Week Toxicity Study in Rats with Administration by the Diet

DP BARCODE: 355254

P.C. CODE: 129028 (E,E-8,10-dodecadien-1-ol)

DECISION NO.: 397560

REGISTRATION NO: 73049-UAN

PRODUCT NAME: S-Abscisic Acid (TGAI)

MRID NO. 474705-10

SPONSOR: Valent Biossciences Corporation
870 Technology Way, Suite 100
Libertyville, IL 60048 USA.

TEST FACILITY: Charles River laboratories
Tranent, Edinburgh EH33 2NE, UK

STUDY SUMMARY:

The objective of this study is to assess the oral toxicity of VBC-30054 (Technical grade S-Abscisic Acid (ABA) administered via oral route for 13 weeks. This study was designed to be compliant with the guidelines of the EU authorities, and is in accordance with the guidelines detailed in the OECD 407 (adopted by the council on 21 September 1998) and OPPTS 870.3100 (July 2000) of the US EPA.

Four groups of 10 male and 10 female Spraque-Dawley rats were dosed continuously by diet for 13 consecutive weeks at levels of 0, 2000, 6000 and 20000 ppm. S-ABA. The animals were 28 days old when they first arrived to the laboratory, and not 6 weeks old as proposed in the study proposal. Since the weights were within required range, this deviation was assumed not to adversely affect the integrity of study results.

Diet formulations were prepared weekly by simple mixing of appropriate weighed quantities of test material to measured weights of diet. Blank diet, without ABA, was prepared for the Control animals. They were analyzed in triplicate samples for concentration, homogeneity and stability. Triplicate samples were taken from each formulated diet (including Control) immediately after preparation in Weeks 1, 6 and 12 to assess concentration. The analyzed concentrations of the formulations were within ± 10% of the nominal indicating acceptable accuracy of formulation.

Animals were housed in grid cages (42 x 27 x 20 cm) from Arrival (17 April 2007) until during Week 4 (25 May 2007). There were incidences throughout the study where animals were temporarily moved into solid bottom cages due to the clinical signs seen. These deviations were considered not to have affected the integrity or outcome of the study. The animals were allowed to acclimate for a period of 17 days before the commencement of dosing. The acclimation period was longer than anticipated due to dietary preparation constraints. This was considered not to have affected the integrity or outcome of the study.

Each cage was supplied with a polycarbonate water bottle with a DurethanTM cap and stainless steel nozzle. Beneath each cage was a suspended tray containing absorbent paper. Paper was changed as necessary. Wooden chewsticks were provided to the animals for environmental enrichment. Cages and hoppers were changed once every 2 week. Water bottles were changed at least once each week.

There was automatic control of temperature and humidity, target ranges were 21°C ± 2°C and 55% ± 15 respectively with a minimum of 15 air changes per hour. It is acknowledged that there was one occasion during Week 2 that the temperature was above the target temperature range as well as one occasion during Week 5 where the humidity was below the target humidity range, but these were considered not to have adversely affected the rats. Light hours were 0700— 1900 h.

Food and water were supplied *at libitum*. Water was analysed at regular intervals for dissolved materials, heavy metals, pesticide residues, pH, nitrates and nitrites, including bacteriological screening. The most recent bacteriological screen undertaken at Charles River Laboratories showed an unusually high level of bacterial colony forming units (cfu) at 37°C (105 cfu/mL). There is considered to be little or no potential effect on human health at levels up to 100 cfu/mL. Due to these factors, and the fact that the animals exhibited no adverse effects which could have been linked to high bacteria levels in the water supply, it was considered not to have affected the integrity or outcome of the study.
The food and water used was considered not to contain any additional substances, in sufficient concentration, to have any influence on the outcome of the study.

Animals were randomly allocated to 4 dose treatment of 0, 2000, 6000 and 20000 ppm. S-ABA The animals were dosed by oral administration for 7 days/week for 13 consecutive weeks. Control animals received blank diet only.

All statistical tests were two-sided and performed at the 5% significance level using in-house software. Males and females were analyzed separately. Pairwise comparisons were only

performed against the control group (Group 1). The following pairwise comparisons were performed:

Control Group vs Low Dose
Control Group vs Intermediate Dose
Control Group vs High Dose

Body weight, food consumption, haematology, clinical chemistry, selected urinalysis and selected neurotoxicity data were analyzed for homogeneity of variance using the 'F-Max' test. If the group variances appeared homogeneous, a parametric ANOVA was used and pairwise comparisons were made using Fisher's F protected LSD method via Student's t test ie pairwise comparisons were made only if the overall F-test is significant. If the variances were heterogeneous, log or square root transformations were used in an attempt to stabilise the variances. If the variances remain heterogeneous, then a Kruskal-Wallis non-parametric ANOVA was used and pairwise comparisons were made using chi squared protection (via z tests, the non-parametric equivalent of Student's t test).
In circumstances where it was not possible to perform the F Max test due to zero standard deviation in at least one group, the non-parametric ANOVA results were reported.
Organ weights were analyzed using ANOVA as above and by analysis of covarianee (ANCOVA) using terminal kill body weight as covariate. In addition, organ weights as a percentage of terminal body weight were analysed using ANOVA as above as an exploratory analysis, but not reported.
In circumstances where the variances in the ANCOVA remain heterogeneous following log or square root transformations or where it was not possible to perform the F-Max test,the untransformed parametric ANCOVA results were reported.
Histological incidence data was analyzed using Fisher's Exact Probability Test.

There were 3 premature death during the period of treatment.
There were no clinical observations attributed to treatment effects.

As all of the clinical signs seen were only observed in the arena and not in the cage, they were thought to be a normal reaction to unfamiliar surroundings and not representative of test item toxicity.

During Week 12 observations, a small number of males treated at 20000 ppm were noted to have reduced response to tactile stimulus and a small number of females treated at> 6000 ppm were noted to have an increased exaggerated reaction or jerks response to tactile stimulus.

There were no notable intergroup differences in motor activity in either sex thought to be related to treatment (Tables 3 and 4, Appendices 9 and 10).

There were no notable intergroup differences in detailed functional observations in either sex thought to be related to treatment (Tables 5-10, Appendices 11-16)

After 13 weeks of treatment males treated at 20000 ppm had slightly reduced group mean bodyweight gain and group mean bodyweight (throughout treatment), both without statistical

significance when compared to the respective controls (Tables 11 and 12, Figures 1 and 2, Appendices 17 and 18). The females also had slightly reduced group mean bodyweight gain (non-statistically significant) when treated at 20000 ppm however no effect was seen in the group mean bodyweights when compared to the controls. No notable findings were seen in males and females treated at 2000 and 6000 ppm

There were sporadic incidences where the food consumption in treated groups was higher or lower when compared to their respective controls, however no pattern was established and therefore was not thought to be a treatment related effect (Tables 13 and 14, Appendices, 20 and 21).

Slightly increased lymphocytes and white blood cell count without statistical significance were noted in females treated at 20000 ppm when compared to the Controls. However due to variance in the individual values this was considered not to be toxicologically significant.
Any other changes in the hematological parameters were considered neither to be significant or treatment related (Tables 15 and 16, Appendices 24 and 25).

Cholesterol appeared to be slightly increased and triglycerides appeared to be decreased, without statistical significance in a dose related pattern in both males and females however the variation within the individual values would indicate that these values are not representative of toxicity. Other sporadic instances of statistically significant increases or decreases were noted in sodium, albumin and calcium however they were not thought to be representative of treatment related toxicity (Tables 17 and 18, Appendices 26 and 27).

There were no changes in urinalysis parameters that were considered to be significant or treatment related (Tables 19 and 20, Appendices 28 and 29).

The covariant liver weights appeared to be slightly increased (without statistical significance) in males treated at 6000 ppm and females treated at 20000 ppm when compared to their respective controls. The absolute and covariant spleen weights were noted to be slightly reduced without statistical significance in the treated males when compared to the controls. The males were also noted to have slightly reduced covariant adrenal gland weights with statistical significance in all treated groups though not in a dose related pattern (Tables 21-24, Appendices 30 and 31).

Females treated at 6000 ppm were also noted to have slightly increased (without statistical significance) covariant thyroid gland weights when compared to the controls.
The slightly increased covariant thymus weight in all treated males (not statistically significant) and the slightly increased covariant ovary weights noted in all treated females (not statistically significant) were thought to be due to lower covariant weights in the Control animals and therefore were considered not to be of toxicological significance.
There were other sporadic instances of slightly increased or decreased organ weights (non-statistically significant) however they were not thought to be indicative of toxicity.

All histology findings were considered to be spontaneously occurring background findings, representative of those found in rats of this age and strain.

Administration of VBC-30054 via the diet for 13 consecutive weeks was associated with non-statistically significant slight reductions in mean body weight gain and group mean bodyweight throughout treatment in males treated with 20000 ppm and non-statistically significant reduction in group mean bodyweight gain in females treated at 20000 ppm. There was no effect on food consumption.

No toxicological significance was given to the small number of males noted to have reduced response to tactile stimulus and with the small number of females noted to have increased response to tactile stimulus as these findings were contradictory and there were no other signs indicative of neurotoxicity in the animals. Therefore the observations seen were not thought to be indicative of toxicity.

Increased covariant liver weights (without statistical significance)noted in males treated at 6000 ppm and females treated at 20000 ppm, correlates with the slight changes noted in cholesterol noted in males, however triglycerides were decreased with no changes seen in the proteins or liver enzymes and so these findings were not conclusive of toxicity. Furthermore, there were no differences noted in the clinical pathology or histopathology of the liver.
All differences noted in the covariant thyroid, liver, pituitary, spleen and adrenal gland weights in males or females (non-statistically significant) were not represented in the clinical pathology or histopathology findings and therefore considered not to be indicative of toxicity from VBC-30054.

In conclusion, under the conditions of this study, the No Observed Adverse Effect Level (NOAEL) was considered to be 20000 ppm, the limit dose.

REVIEWER COMMENTS:

In general, the study is acceptable. The following observations do not constitute major deficiencies likely to compromise study results:

There is no description of randomization procedures for allocation of animals to treatments.
No detail is provided concerning whether females were nullliparous and nonpregnant.
Light cycle was 7:19 h. rather than 12:12 hours, as recommended by OPPTS 870.3100 guidelines.

There is no satellite group as recommended by OPPTS 870.3100 guidelines. A group of 10 males and 10 females, treated at the highest dose should have been observed for no less than 28 days post treatment. There is no indication in the study report that this was done. The reviewer assumes that this was not done due to reported lack of toxicity

The data may be analyzed for determination of a trend. Dose treatments are continuous variables that could have been appropriately analyzed using regression analysis to determine whether a dose trend is statistically significant for any of the measured endpoints. Furthermore, instead of males and females being analyzed separately, a factorial analysis should have been appropriate to determine any statistically significant interaction between treatments and gender.

EPA Primary Reviewer: Clara Fuentes, Ph.D., Entomologist

Date: Nov. 17, 2009

NOV 17 2009

Data Evaluation Record

STUDY TYPES: A Prenatal Developmental Toxicity Study of S-Abscisic Acid in Rats.

DP BARCODE: 355254

P.C. CODE: 129028 (E,E-8,10-dodecadien-1-ol)

DECISION NO.: 397560

REGISTRATION NO: 73049-UAN

PRODUCT NAME: S-ABSCISIC ACID (S-ABA)

MRID NO. 474705-12

SPONSOR: Valent Biossciences Corporation
870 Technology Way, Suite 100
Libertyville, IL 60048 USA.

TEST FACILITY: WIL Ressearch Laboratories, LLC.
1407 George Road
Ashland, OH. 44805-8946

STUDY SUMMARY

The objective of the study is to evaluate the potential of VBC-Abscisic acid Technical Grade Active Ingredient to induce developmental toxicity after maternal exposure during the critical period of organogenesis, and characterize maternal toxicity to determine a no adverse effect level (NOAEL).

Three dose levels (500, 750, and 1000 mg/kg/day) of VBC-30054 were assigned to separate groups of 25 female rats per group. The doses were within ± 2% of their nominal concentrations, and stable for 10 days of refrigerated storage. A fourth control group of 25 females received a comparable treatment of 0.5% methylcellulose with no VBC-30054. The

number of animals used for testing was based on US EPA Health Effects Test Guidelines OPPTS 870.3700, Prenatal Developmental Toxicity Study (1998), and OECD Guidelines for Testing of Chemicals Guidelines 414, Prenatal Development Toxicity Study (2001).

The experiment was a randomized block design consisting of 4 dose treatment groups, including one control group, of 25 females each. Females were stratified by body weights on their gestation day 0 and randomized into blocks. Minimum significance levels were set at $P \leq 0.01$ and 0.05 % . Treatments were compared to control using 2-tailed tests when overall F was significant in a one way ANOVA analysis. Each mean was reported with its associated standard deviation and standard error. Fetal endpoints measured were analyzed using Kruskal-Wallis nonparametric ANOVA procedure.

The rats were approximately 70 days old when received in the laboratory, and 90 days old at initiation of the test. Females were selected for the test based on acceptable health and weight. The selected females were approximately 12 weeks old when paired for breeding. Mating was confirmed by presence of vaginal copulatory plug or sperm. Doses of VBC-30054 in 0.5% methylcellulose were administered orally once a day via gavage at a dose volume of 10 mL/kg, from gestation days 6 to 19. All animals were killed on day 20 for further examination.

All animals were observed twice daily for vitality, once in the morning and once in the afternoon during duration of the test. Animals were also monitored 1 hour following dose administration. Clinical observations, body weights and food consumption were recorded. On gestation day 20, a laparohysterectomy was performed on each female. Uteri and ovaries were examined, and the number of fetuses, early and late resorptions, total implantations, corpora lutea, gravid uterine weights and net body weights were recorded. The fetuses were examined for malformations and developmental variations. All observations were recorded blind of test group.

No dose related effect on maternal body weight, food consumption, post implantation losses, size of live litters, mean fetal weight, fetal sex rates, fetal malformations or developmental variations were observed to be attributed to dose treatments. Based on these results, NOAEL level was set at 1000 mg/kg/day.

REVIEWER COMMENTS

The study is acceptable.
There was 100% maternal survival. Maternal clinical observations include the presence of yellow and red materials on anogenital area of females at the highest doses, 750 and 1000 mg/kg/day, on gestation days 16 to 19, and sporadic incidences of clear and red materials around the mouth 1 hour post dose treatment at doses 750 and 1000 mg/kg/day, starting as early as gestation day 6. These incidents were considered test-article related and not dose related, and not adverse. However, these incidents only occurred at the highest doses, and thus, they should be discussed further.

EPA Primary Reviewer: Clara Fuentes, Ph.D., Entomologist

Date: Nov. 17, 2009

Data Evaluation Record

STUDY TYPES: VBC-30054 Reporter Gene Assays for Abscisic Acid (ABA) Using Human Estrogen and Androgen Receptors.

DP BARCODE: 355254

P.C. CODE: 129028 (E,E-8,10-dodecadien-1-ol)

DECISION NO.: 397560

REGISTRATION NO: 73049-UAN

PRODUCT NAME: S-ABSCISIC ACID (S-ABA)

MRID NO. 474705-13

SPONSOR: Valent Biossciences Corporation
870 Technology Way, Suite 100
Libertyville, IL 60048 USA.

TEST FACILITY: Environmental Health Science laboratory
Sumitomo Chemical Co. Ltd.
I-98, 3-Chome, Kasugade-Naka
Konohana-Ku. Osaka, Japan

STUDY SUMMARY:

The objective of the study was to evaluate estrogenic, anti-estrogenic, androgenic and anti-androgenic effects of ABA using mammalian cell-based luciferase reporter.

Estrogenic, anti-estrogenic, androgenic and anti-androgenic activities of absicic acid were evaluated using receptor- mediated assays in vitro. Mammalian cell-based luciferase reporter gene assays were developed for detecting the effects of ABA on human estrogen receptor α

(hERα) or androgen receptor (hAR) mediated transactivation. Cells expressing luciferase constitutively were used for estimating effects of chemicals on transcriptional activity by a receptor-independent manner or cytotoxicity.

Marked positive effects of estradiol (E2) and dihydrotestosterone (DHT) were detected by hER α and hAR assays, respectively. Anti-estrogen, 4-hydroxytamoxifen (HTM) and anti-androgen, hydroflutamide (HFT) inhibited the E2 and DHT-mediated transactivation, respectively. Differences were tested for statistical significance at $p < 0.05$, using t-test computed by Excel (Microsoft). However, no significamt estrogenic, anti-estrogenic, androgenic or anti-androgenic effect of ABA was found by the assays (1 nM-10 μM), suggesting that ABA does not impact on hER α and hAR-mediated transactivation pathways in vitro.

Following exposure to E2 (1 μM), cells transfected with hER α showed induction of about 12-fold relative to solvent control in the mammalian cell-based luciferase reporter gene assay. No significant ($p < 0.05$) ligand-dependent activations of luciferase was found with ABA . Anto-estrogen (4-hydroxytamoxifen) markedly inhibited E2-mediated luciferase inductions. However, no significant effects were detected by treatment with ABA. In these assays, ABA did not show any citotoxicity or transactivational activity in a receptor-independent manner. Cells transfected with hAR showed marked induction of about 70 fold relative to solvent control by treatment with DHT (1 μM). No significant ligand-dependent activation of luciferase was appeared with ABA. Anti-androgen (hydroxyflutamide) markedly inhibited DHT-mediated luciferase inductions. However, no significant effects were detected with ABA. In these assay, ABA did not show any cytotoxicity or transactivational activity in a receptor-independent manner.

These results indicate that ABA is not capable of affecting ER α and AR mediated transcativational in vitro. Therefore, it can be concluded that ABA is not an estrogenic, anti-estrogenic, androgenic or anti-androgenic compound.

REVIEWER COMMENTS:

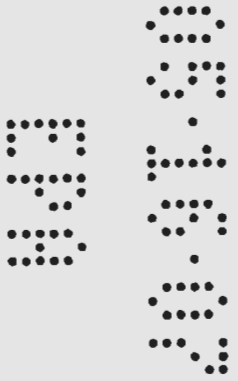
Acceptable.

Study Title
S-Abscisic Acid (S-ABA)
Justification for Requesting a Waiver from the
Biochemical Pesticide Data Requirements for
Non-Target Plant Testing
For Experimental Use Permits for S-Abscisic Acid

Data Requirements
OPPTS 850.4000
OPPTS 850.4200
OPPTS 850.4400

Author
Thomas Bade

Paper Completed on
May 9, 2007



Author Address
Valent BioSciences Corp.
870 Technology Way
Libertyville, IL. 60048

Project ID
S-ABA 30054; 047-02

Pages 181-195 Access to Registration Data is Restricted Under FIFRA section 10(g)

DATA PACKAGE BEAN SHEET

Date: 31-Jul-2008

Decision #: 397560
DP #: (355137)
PRIA
Parent DP #:
Submission #: 832265

* * * Registration Information * * *

Registration: 73049-UAN - S-ABSCISIC ACID, (S-ABA) TECHNICAL GRADE ACTIVE IN

Company: 73049 - VALENT BIOSCIENCES CORPORATION

Risk Manager: RM 91 - Driss Benmhend - (703) 308-9525 Room# PY1 S-8948

Risk Manager Reviewer: Jay Pfeifer JPFEIFER

Sent Date: _____ Calculated Due Date: 21-Nov-2009 Edited Due Date: _____

Type of Registration: Product Registration - Section 3

Action Desc: (B590) NEW AI;FOOD USE;MICROBIAL/BIOCHEMICAL WITH EXEMPTION;

Ingredients: 272000, Abscisic acid(99.3%)

* * * Data Package Information * * *

Expedite: ● Yes ○ No Date Sent: 31-Jul-2008 Due Back: _____

DP Ingredient: 272000, Abscisic acid

DP Title: Tox

CSF Included: ● Yes ○ No Label Included: ● Yes ○ No Parent DP #: _____

	Assigned To	Date In	Date Out	
Organization:	BPPD / BPB	31-Jul-2008		Last Possible Science Due Date: 29-Jul-2008
Team Name:	RM 91	31-Jul-2008		Science Due Date:
Reviewer Name:	Alam, Wagi	04-Aug-2008		Sub Data Package Due Date:
Contractor Name:				

* * * Studies Sent for Review * * *

Printed on Page 2

* * * Additional Data Package for this Decision * * *

Printed on Page 3

* * * Data Package Instructions * * *

Please Expedite. This is being done as part of a joint review with Australia, and must be done ASAP.

Review Tox for Acceptability of New AI / Food Use

MRID	MRID Status	Citation	Guideline
47470507		Shearer, J. (2008) VBC-30054: One Week Dose Range Finding Study in Rats with Dermal Administration: Final Report. Project Number: 27954, 458194. Unpublished study prepared by Charles River Laboratories. 58 p.	
47470508		Shearer, J. (2008) VBC-30054: 3 Week Toxicity Study in Rats with Dermal Administration: Final Report. Project Number: 27971, 458215. Unpublished study prepared by Charles River Laboratories. 177 p.	
47470509		Perry, C. (2008) VBC-30054: 4 Week Toxicity Study in Rats with Administration by the Diet: Final Report. Project Number: 27720, 457866. Unpublished study prepared by Charles River Laboratories . 223 p.	
47470510		Perry, C. (2008) VBC-30054: 13 Week Toxicity Study in Rats with Administration by the Diet: Final Report. Project Number: 457871, 28084. Unpublished study prepared by Charles River Laboratories . 280 p.	

DATA PACKAGE BEAN SHEET

Date: 31-Jul-2008

Decision #: 397560
DP #: (355133)
PRIA
Parent DP #:
Submission #: 832265

* * * Registration Information * * *

Registration: 73049-UAN - S-ABSCISIC ACID, (S-ABA) TECHNICAL GRADE ACTIVE IN

Company: 73049 - VALENT BIOSCIENCES CORPORATION

Risk Manager: RM 91 - Driss Benmhend - (703) 308-9525 Room# PY1 S-8948

Risk Manager Reviewer: Jay Pfeifer JPFEIFER

Sent Date: _____ Calculated Due Date: 21-Nov-2009 Edited Due Date: _____

Type of Registration: Product Registration - Section 3

Action Desc: (B590) NEW AI;FOOD USE;MICROBIAL/BIOCHEMICAL WITH EXEMPTION;

Ingredients: 272000, Abscisic acid(99.3%)

* * * Data Package Information * * *

Expedite: ○ Yes ● No Date Sent: 31-Jul-2008 Due Back: _____

DP Ingredient: 272000, Abscisic acid

DP Title: Chem/Eco 2nd Material

CSF Included: ● Yes ○ No Label Included: ● Yes ○ No Parent DP #: _____

	Assigned To	Date In	Date Out	
Organization:	BPPD / BPB	31-Jul-2008		Last Possible Science Due Date: 29-Jul-2008
Team Name:	RM 91	31-Jul-2008		Science Due Date:
Reviewer Name:	Jones, Russell		31-Jul-2008	Sub Data Package Due Date:
Contractor Name:				

* * * Studies Sent for Review * * *

Printed on Page 2

* * * Additional Data Package for this Decision * * *

No Additional Data Packages

* * * Data Package Instructions * * *

Hold until Australia does Primary

47470401	Rose, J. (2007) Analysis and Certification of Product Ingredients in Five Batches of Technical S-Abscisic Acid. Project Number: 1473W. Unpublished study prepared by PTRL West, Inc. 122 p.	
47470403	Bade, T. (2008) S-Abscisic Acid: VBC-30054 Technical Powder Product Chemistry: Certification of Limits. Project Number: S/ABA/30054, 127/2. Unpublished study prepared by Valent Biosceinces Corporation. 11 p.	151-15/Certification of Ingredient Limits
47470403	Bade, T. (2008) S-Abscisic Acid: VBC-30054 Technical Powder Product Chemistry: Certification of Limits. Project Number: S/ABA/30054, 127/2. Unpublished study prepared by Valent Biosceinces Corporation. 11 p.	830.1750/Certified limits
47470406	Ponte, M.; Schick, M. (2007) Stability of S-Abscisic Acid Active Ingredient to Normal and Elevated Temperature, Metals, and Metal Ions, and Oxidizing Reducing Properties of S-Abscisic Acid Active Ingredient. Project Number: 1618W, 1618W/1. Unpublished study prepared by PTRL West, Inc. 59 p.	830.6313/Stability to sunlight, normal and elevated temperatures, metals, and metal ions
47470406	Ponte, M.; Schick, M. (2007) Stability of S-Abscisic Acid Active Ingredient to Normal and Elevated Temperature, Metals, and Metal Ions, and Oxidizing Reducing Properties of S-Abscisic Acid Active Ingredient. Project Number: 1618W, 1618W/1. Unpublished study prepared by PTRL West, Inc. 59 p.	830.6314/Oxidizing or reducing action
47470410	Comb, A. (2007) VBC-30054 Physico-Chemical Properties. Project Number: ZAB/0083. Unpublished study prepared by Huntingdon Life Sciences, Ltd. 36 p.	111-222/
47470410	Comb, A. (2007) VBC-30054 Physico-Chemical Properties. Project Number: ZAB/0083. Unpublished study prepared by Huntingdon Life Sciences, Ltd. 36 p.	830.6315/Flammability
47470410	Comb, A. (2007) VBC-30054 Physico-Chemical Properties. Project Number: ZAB/0083. Unpublished study prepared by Huntingdon Life Sciences, Ltd. 36 p.	880.1100/Product identity and composition
47470411	Schick, M. (2008) Solubility of S-Abscisic Acid in Organic Solvents. Project Number: 1730W, 1730W/1. Unpublished study prepared by PTRL West, Inc. 52 p.	830.7840/Water solubility: Column elution method, shake flask method
47470412	Schick, M. (2008) Hyrolysis of S-Abdscisic Acid at pH 4, 7, and 9. Project Number: 1729W, 1729W/1. Unpublished study prepared by PTRL West, Inc. 89 p.	835.2110/Hydrolysis as a function of pH
47470413	Shi, L. (2004) Evaluation of the Environmental Safety of S-Abscisic Acid. Project Number: 2004B/04. Unpublished study prepared by Nanjing Institute of Environmental Sciences. 59 p.	
47470414	Zhang, H. (2004) Certification of S-ABA Reference Standard (Lot # 030806D1): Laboratory Final Report. Project Number: VAL0105DX, REP/RC/2004/048. Unpublished study prepared by deCode Chemistry, Inc. 75 p.	830.1550/Product Identity and composition
47470415	Zhang, H. (2005) Retest of S-ABA Reference Standard (Lot # 030806D1). Project Number: VAL0107DX, REP/RC/2005/039. Unpublished study prepared by deCode Chemistry, Inc. 27 p.	830.1550/Product Identity and composition

Australian Government

Department of the Environment, Water, Heritage and the Arts

FILE NO 2008/12802
CONTACT D Murphy
PHONE (02) 6274 2201

Ms Margot Davis
Regulatory Officer
Valent BioSciences
PO Box 5125
CHATSWOOD NSW 1515

Dear Ms Davis

S-ABSCISIC ACID - INTERNATIONAL WORK SHARE
PROTONE® SG PLANT GROWTH REGULATOR
APVMA NUMBERS: NCRIS 63314 AND ATS 45309

As you are aware, DEWHA has been assessing the environmental data package provided by Valent BioSciences in support of the above International Work Share application.

The aspect DEWHA has had to look at very carefully during its assessment of the environmental fate and effects is the claim for a waiver of many of the standard test requirements based on the argument that abscisic acid is a natural product and therefore many organisms will have been already exposed to it in the environment. While this is true, DEWHA's examination has revealed that natural levels in plants and in soil are at a much lower level than when abscisic acid is sprayed onto grape vines at the high proposed rate of up to 1000 g/ha.

Based on these very high unnatural levels DEWHA has had to examine all the claims for waivers of test requirements much more closely and, in many cases, do a *de facto* risk assessment using conservative assumptions. While this has supported many of claims for a waiver, there are a number of areas where some greater detail or clarification would greatly assist our assessment. Our initial assessment of the fate and ecotoxicity of S-abscisic has been loaded as draft reports onto CIRCA database and notified to the other regulatory agency involved in this international work share, the US EPA, for their consideration. In the interim your attention to the issues identified in Attachment 1 to this letter would greatly help with the finalisation of this part of the assessment.

Should you wish to discuss these matters further, please do not hesitate in contacting us.

Yours sincerely

Greg Plummer
Director
Chemical Assessment Section

3 December 2009

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Cc: Dr Vanessa Burgess
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Janet Anderson
Director, Biopesticides and Pollution Prevention Division
Office of Pesticide Programs
US EPA
1200 Pennsylvania Avenue, NW
Washington, DC 20460
The United States of America

Attachment 1

Valent BioSciences is asked to consider the following issues and to appropriately respond to them with either data or scientifically based argument. The items are identified by the appropriate OECD classification number.

1. IIA 2.9.2 Direct phototransformation of purified active substance in water using artificial light

Study: Shi *et al.* (2004)
This study is currently rated as "3" or "Not reliable" [See attachment 2 for a listing of the rating categories]. Confirmation that a 290 nm filter was used, clarification of the light intensity plus comment on the possible formation of photodegradation products in the aquatic photolysis test could allow assignment as a 2* reliability compared with its current 3 rating.

A Xenon lamp of 1000 W was said to be used as the light source with a light intensity of 3.4×10^3 Lux and ultraviolet intensity at 45 W/cm^2. This appears very intense. With respect to this last value, the Chinese report refers to a value of "45.0 uw/cm^2" and it is not immediately clear as to what the actual intensity was. Clarification of this matter would be appreciated.

Advice should be provided as to whether degradation products were investigated, and if so, was mainly the cis/trans S-ABA isomer formed?

If degradation products were not investigated, please comment on what would be expected?

With regard to this issue, the applicant's attention is drawn to Johnson (1980) in which the photoisomerization kinetics of the geometric isomers of abscisic acid in solution and in seedlings of Douglas-fir was considered with a conclusion reached that photolysis at 254 nm resulted in rapid isomerisation (cis/trans to trans/trans) and further photolysis, i.e. degradation of the S-ABA or its photoisomers. In contrast, photolysis at sunlight wavelengths results essentially in the cis/trans and trans/trans interconversion.

Clarification of the photolytic fate of S-ABA in water is a key concern given its stability to hydrolysis and the absence of a standard aerobic sediment/water metabolism study in the data package.

2. IIA 7.1.1 Aerobic degradation (in soil)

Study: Shi *et al.* (2004)
While the summary of soil degradation presented by Shi *et al.* indicates S-ABA degrades readily in soil, the absence of detail on the degradation products remains a data gap if tested to OECD 307 (Aerobic and Anaerobic Transformation in Soil). However, Hartung *et al.* (1996) have reported that when compost soil was incubated with [^{14}C]-ABA, 30-40% of the ABA was metabolized after 72 hours and two metabolites, phaseic acid and dihydrophaseic acid, identified. Based on the findings of Hartung *et al.* (1996) and also of Zeevaart and Yang (undated), it could be that, in soil, phaseic and dihydrophaseic acids are the ultimate degradation products. Consequently, the absence of soil degradates

in Shi's summary of the soil degradation of abscisic acid, is possibly covered by information in the literature provided.

Valent BioSciences is asked to clarify whether degradation products were investigated, and if not, whether dihydrophaseic acid is the ultimate end point of soil metabolism, or whether it degrades/mineralizes further.

3. IIA 7.8 Degradation in aquatic systems

Due to the lack of a test, the route of degradation and ultimate fate of S-ABA in natural waterbodies remains unclear. Based on its solubility, it is expected to remain in the water column. However, photolysis is considered to be likely to occur (with at least photoisomerisation to the less active isomer occurring), with an associated lowering of the concentration of the S-ABA in the water column.

While turbidity and water depth could reduce the effectiveness of photolytic dissipation, the role metabolism would play is unclear, though it is Australia's experience that metabolism/degradation in the water column is generally slower than in soil.

Therefore, it may be expected that S-ABA will be more persistent in the water column than is indicated by the soil metabolism results and the applicant's attention is drawn to the fact that conservative assumptions will need to be made in the risk assessment in the absence of test data.

4. IIIA 10 Ecotoxicological Studies on the Plant Protection Product.
(IIIA 10.8.1.2 Vegetative Vigor and IIIA 10.8.1.3 Seedling Emergence)

Studies: Porch *et al.* (2008a) [Wildlife Int. Project Number: 529-115] and (2008c) [Wildlife Int. Project Number: 529-116]

The two plant phytotoxicity studies were conducted as limit tests according to appropriate US EPA and/or OECD guidelines. While satisfactorily conducted, the main problem with the two plant tests may have been that the proposed Australian formulation was not used, and more importantly, that no surfactant was used as directed on the Australian draft label. As the surfactant is generally used to ensure the active gets into the plant (e.g. as with glyphosate and many other herbicides) to be effective, this could be a major deficiency and the tests may not properly reflect the actual phytotoxicity that could be seen if applied as proposed. This is a significant matter as the US OPPTS guidelines followed (OPPTS 850.4100, Terrestrial Plant Toxicity, Tier I (Seedling Emergence) and 850.4150, Terrestrial Plant Toxicity, Tier I (Vegetative Vigor)) state they should be used in conjunction with OPPTS guideline 850.4000 (Background-Nontarget Plant Testing). This latter guideline states that, "If an adjuvant is recommended on the product label, representative adjuvants must be included in the test at the recommended dosage.", which does not appear to be the case with the two phytotoxicity studies considered.

Further, as abscisic acid is involved in plant reproduction (see for example, in the Valent BioSciences' report summary for Metabolism, page 3 of 48 where Petracek *et al.* (2008) state that, "ABA is involved in many major processes during plant growth and development including dormancy, germination, **bud break, flowering, fruit set***, general growth and development, stress tolerance, ripening, maturation, organ abscission,

and senescence." is quoted), the question is raised as whether the standard testing covered such aspects. Further, it is noted that in the vegetative vigor study the time between planting and treatment was 14 to 23 days rather than the 4 to 6 weeks (28 to 42 days) recommended by OPPTS guideline 850.4150 and it is queried whether the early treatments used would have allowed effects of S-abscisic on such processes to have been observed.

Some aspects of reproduction would have been considered in the studies, e.g. most obviously with seed dormancy as shown by the inhibition of germination during the test. Inhibition of cell division is another aspect, probably covered in the tests. However, there seems to be no indication as to whether plants (those that would) developed buds, flowered or if fruit set during the 21-28 d tests performed.

Given the importance of these effects on non-target vegetation of this plant hormone, the applicant's comments and advice on these apparent deficiencies in the phytotoxicity tests are requested.

* DEWHA's emphasis.

5. IIA 8.8 Effects on non-target terrestrial arthropods

Standard studies addressing the effect of S-ABA on non-target terrestrial arthropods were not submitted. As a result it is not known whether the proposed use would have untoward effects on these, including any integrated pest management practices (IPM) being conducted in the treated vineyards.

Consequently, the implications for a waiver of the non-target terrestrial arthropod tests is still unclear, particularly given honey bees (the only non-target terrestrial arthropod species tested) are not considered by DEWHA as good surrogates for these. Advice as to the extent of IPM in Australian vineyards and the potential effects of S-ABA on these practices is required.

A related issue is whether in fact bunch directed spraying is mandated or simply recommended as currently reflected in the draft Australian label. This is another issue on which clarification is sought as the application has referred to this practice reducing the exposure to non-target species.

Hartung, W., A. Sauter, N. C. Turner, I. Fillery and H. Heilmeier (1996). Abscisic acid in soils: What is its function and which factors and mechanisms influence its concentration?, Plant Soil. 184: 105-110.

Johnson, J. D. (1980). Environmental and Physiological Control of Stomates in Douglas-fir and Other Species. A THESIS submitted to Oregon State University in partial fulfilment of the requirements for the degree of Doctor of Philosophy Completed December 16, 1980 Commencement June 1981. Located at http://ir.library.oregonstate.edu/jspui/bitstream/1957/10929/1/Johnson_Jon_Dale_1980.pdf.

Zeevaart, J. A. D. and Yang, S-H (undated). Abscisic Acid Metabolism. Accessed on 19 October 2009 at http://www.pgrsa.org/2005_Proceedings/papers/001.pdf.

Attachment 2

The system used to rate study reliability

The rating system used in the Australian assessment of the studies provided or obtained in support of the application for Protone SG is as set out in the Environmental Risk Assessment Guidance Manual for agricultural and veterinary chemicals*, which, in section 4.2.1 Data Reliability Assessment, states:

The reliability of the data is a key initial consideration because without knowledge of how the study has been conducted all other considerations may be irrelevant. Screening for reliability can be done relatively quickly to filter out unreliable studies and enable the risk assessor to focus further resources on those studies considered most reliable.

The following approach for determining reliability is used by DEWHA:

1 Fully reliable:	GLP compliant and fully compliant with the Test Guideline specified.
2 Reliable with restrictions:	GLP compliant but not fully compliant with the Test Guideline specified, but nevertheless judged to provide a reliable basis for regulatory decision-making. An asterisk is to be added to identify studies that are not standard that are judged to be reliable for the purpose conducted (e.g. mechanistic studies)
3 Not reliable:	Not GLP compliant and/or not compliant with the Test Guideline specified, and judged to not provide a reliable basis for regulatory decision-making.
4 Not assignable:	Insufficient information provided to allow the reliability of the test or study report to be assessed (e.g. published literature).

It should be noted, these ratings are derived from the OECD. Australia does not have mandatory GLP and consequently some allowances need to be made in addressing the validity of a study. For example, non-GLP studies can not be considered unreliable on these grounds alone. Therefore, a degree of expert judgement has been used in applying the validity rankings associated with studies assessed.

* Accessible via http://www.ephc.gov.au/taxonomy/term/75

Australian Government

Department of the Environment, Water, Heritage and the Arts

FILE NO 2008/12802
CONTACT D Murphy
PHONE (02) 6274 2201

Ms Margot Davis
Regulatory Officer
Valent BioSciences
PO Box 5125
CHATSWOOD NSW 1515

Dear Ms Davis

S-ABSCISIC ACID - INTERNATIONAL WORK SHARE
PROTONE® SG PLANT GROWTH REGULATOR
APVMA NUMBERS: NCRIS 63314 AND ATS 45309

As you are aware, DEWHA has been assessing the environmental data package provided by Valent BioSciences in support of the above International Work Share application.

The aspect DEWHA has had to look at very carefully during its assessment of the environmental fate and effects is the claim for a waiver of many of the standard test requirements based on the argument that abscisic acid is a natural product and therefore many organisms will have been already exposed to it in the environment. While this is true, DEWHA's examination has revealed that natural levels in plants and in soil are at a much lower level than when abscisic acid is sprayed onto grape vines at the high proposed rate of up to 1000 g/ha.

Based on these very high unnatural levels DEWHA has had to examine all the claims for waivers of test requirements much more closely and, in many cases, do a *de facto* risk assessment using conservative assumptions. While this has supported many of claims for a waiver, there are a number of areas where some greater detail or clarification would greatly assist our assessment. Our initial assessment of the fate and ecotoxicity of S-abscisic has been loaded as draft reports onto CIRCA database and notified to the other regulatory agency involved in this international work share, the US EPA, for their consideration. In the interim your attention to the issues identified in Attachment 1 to this letter would greatly help with the finalisation of this part of the assessment.

Should you wish to discuss these matters further, please do not hesitate in contacting us.

Yours sincerely

Greg Plummer
Director
Chemical Assessment Section

3 December 2009

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PO Box 6182
KINGSTON ACT 2604

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Senior Evaluator
Australian Pesticides and Veterinary Medicines Authority
PO Box 6182
KINGSTON ACT 2604

~~Janet Anderson~~ Chris Pfeifer
~~Director~~, Biopesticides and Pollution Prevention Division
Office of Pesticide Programs
US EPA
1200 Pennsylvania Avenue, NW
Washington, DC 20460
The United States of America

Attachment 1

Valent BioSciences is asked to consider the following issues and to appropriately respond to them with either data or scientifically based argument. The items are identified by the appropriate OECD classification number.

1. IIA 2.9.2 Direct phototransformation of purified active substance in water using artificial light

Study: Shi *et al.* (2004)
This study is currently rated as "3" or "Not reliable" [See attachment 2 for a listing of the rating categories]. Confirmation that a 290 nm filter was used, clarification of the light intensity plus comment on the possible formation of photodegradation products in the aquatic photolysis test could allow assignment as a 2* reliability compared with its current 3 rating.

A Xenon lamp of 1000 W was said to be used as the light source with a light intensity of 3.4×10^3 Lux and ultraviolet intensity at 45 W/cm^2. This appears very intense. With respect to this last value, the Chinese report refers to a value of "45.0 uw/cm^2" and it is not immediately clear as to what the actual intensity was. Clarification of this matter would be appreciated.

Advice should be provided as to whether degradation products were investigated, and if so, was mainly the cis/trans S-ABA isomer formed?

If degradation products were not investigated, please comment on what would be expected?

With regard to this issue, the applicant's attention is drawn to Johnson (1980) in which the photoisomerization kinetics of the geometric isomers of abscisic acid in solution and in seedlings of Douglas-fir was considered with a conclusion reached that photolysis at 254 nm resulted in rapid isomerisation (cis/trans to trans/trans) and further photolysis, i.e. degradation of the S-ABA or its photoisomers. In contrast, photolysis at sunlight wavelengths results essentially in the cis/trans and trans/trans interconversion.

Clarification of the photolytic fate of S-ABA in water is a key concern given its stability to hydrolysis and the absence of a standard aerobic sediment/water metabolism study in the data package.

2. IIA 7.1.1 Aerobic degradation (in soil)

Study: Shi *et al.* (2004)
While the summary of soil degradation presented by Shi *et al.* indicates S-ABA degrades readily in soil, the absence of detail on the degradation products remains a data gap if tested to OECD 307 (Aerobic and Anaerobic Transformation in Soil). However, Hartung *et al.* (1996) have reported that when compost soil was incubated with [^{14}C]-ABA, 30-40% of the ABA was metabolized after 72 hours and two metabolites, phaseic acid and dihydrophaseic acid, identified. Based on the findings of Hartung *et al.* (1996) and also of Zeevaart and Yang (undated), it could be that, in soil, phaseic and dihydrophaseic acids are the ultimate degradation products. Consequently, the absence of soil degradates

in Shi's summary of the soil degradation of abscisic acid, is possibly covered by information in the literature provided.

Valent BioSciences is asked to clarify whether degradation products were investigated, and if not, whether dihydrophaseic acid is the ultimate end point of soil metabolism, or whether it degrades/mineralizes further.

3. IIA 7.8 Degradation in aquatic systems

Due to the lack of a test, the route of degradation and ultimate fate of S-ABA in natural waterbodies remains unclear. Based on its solubility, it is expected to remain in the water column. However, photolysis is considered to be likely to occur (with at least photoisomerisation to the less active isomer occurring), with an associated lowering of the concentration of the S-ABA in the water column.

While turbidity and water depth could reduce the effectiveness of photolytic dissipation, the role metabolism would play is unclear, though it is Australia's experience that metabolism/degradation in the water column is generally slower than in soil.

Therefore, it may be expected that S-ABA will be more persistent in the water column than is indicated by the soil metabolism results and the applicant's attention is drawn to the fact that conservative assumptions will need to be made in the risk assessment in the absence of test data.

4. IIIA 10 Ecotoxicological Studies on the Plant Protection Product.
(IIIA 10.8.1.2 Vegetative Vigor and IIIA 10.8.1.3 Seedling Emergence)

Studies: Porch *et al.* (2008a) [Wildlife Int. Project Number: 529-115] and (2008c) [Wildlife Int. Project Number: 529-116]

The two plant phytotoxicity studies were conducted as limit tests according to appropriate US EPA and/or OECD guidelines. While satisfactorily conducted, the main problem with the two plant tests may have been that the proposed Australian formulation was not used, and more importantly, that no surfactant was used as directed on the Australian draft label. As the surfactant is generally used to ensure the active gets into the plant (e.g. as with glyphosate and many other herbicides) to be effective, this could be a major deficiency and the tests may not properly reflect the actual phytotoxicity that could be seen if applied as proposed. This is a significant matter as the US OPPTS guidelines followed (OPPTS 850.4100, Terrestrial Plant Toxicity, Tier I (Seedling Emergence) and 850.4150, Terrestrial Plant Toxicity, Tier I (Vegetative Vigor)) state they should be used in conjunction with OPPTS guideline 850.4000 (Background-Nontarget Plant Testing). This latter guideline states that, "If an adjuvant is recommended on the product label, representative adjuvants must be included in the test at the recommended dosage.", which does not appear to be the case with the two phytotoxicity studies considered.

Further, as abscisic acid is involved in plant reproduction (see for example, in the Valent BioSciences' report summary for Metabolism, page 3 of 48 where Petracek *et al.* (2008) state that, "ABA is involved in many major processes during plant growth and development including dormancy, germination, **bud break, flowering, fruit set***, general growth and development, stress tolerance, ripening, maturation, organ abscission,

and senescence." is quoted), the question is raised as whether the standard testing covered such aspects. Further, it is noted that in the vegetative vigor study the time between planting and treatment was 14 to 23 days rather than the 4 to 6 weeks (28 to 42 days) recommended by OPPTS guideline 850.4150 and it is queried whether the early treatments used would have allowed effects of S-abscisic on such processes to have been observed.

Some aspects of reproduction would have been considered in the studies, e.g. most obviously with seed dormancy as shown by the inhibition of germination during the test. Inhibition of cell division is another aspect, probably covered in the tests. However, there seems to be no indication as to whether plants (those that would) developed buds, flowered or if fruit set during the 21-28 d tests performed.

Given the importance of these effects on non-target vegetation of this plant hormone, the applicant's comments and advice on these apparent deficiencies in the phytotoxicity tests are requested.

* DEWHA's emphasis.

5. IIA 8.8 Effects on non-target terrestrial arthropods

Standard studies addressing the effect of S-ABA on non-target terrestrial arthropods were not submitted. As a result it is not known whether the proposed use would have untoward effects on these, including any integrated pest management practices (IPM) being conducted in the treated vineyards.

Consequently, the implications for a waiver of the non-target terrestrial arthropod tests is still unclear, particularly given honey bees (the only non-target terrestrial arthropod species tested) are not considered by DEWHA as good surrogates for these. Advice as to the extent of IPM in Australian vineyards and the potential effects of S-ABA on these practices is required.

A related issue is whether in fact bunch directed spraying is mandated or simply recommended as currently reflected in the draft Australian label. This is another issue on which clarification is sought as the application has referred to this practice reducing the exposure to non-target species.

Hartung, W., A. Sauter, N. C. Turner, I. Fillery and H. Heilmeier (1996). Abscisic acid in soils: What is its function and which factors and mechanisms influence its concentration?, Plant Soil. 184: 105-110.

Johnson, J. D. (1980). Environmental and Physiological Control of Stomates in Douglas-fir and Other Species. A THESIS submitted to Oregon State University in partial fulfilment of the requirements for the degree of Doctor of Philosophy Completed December 16, 1980 Commencement June 1981. Located at http://ir.library.oregonstate.edu/jspui/bitstream/1957/10929/1/Johnson_Jon_Dale_1980.pdf.

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4 Not assignable:	Insufficient information provided to allow the reliability of the test or study report to be assessed (e.g. published literature).

It should be noted, these ratings are derived from the OECD. Australia does not have mandatory GLP and consequently some allowances need to be made in addressing the validity of a study. For example, non-GLP studies can not be considered unreliable on these grounds alone. Therefore, a degree of expert judgement has been used in applying the validity rankings associated with studies assessed.

* Accessible via http://www.ephc.gov.au/taxonomy/term/75

1. Chemistry data review for the approval of a technical grade of active ingredient (TGAI): *S*-abscisic acid

Date: 21 May 2009
APVMA File Number: 63345
Application Number: 45408
Active Ingredient: *S*-Abscisic acid

EPA File Symbol No.:
Product Name:
Active Ingredient: *S*-Abscisic acid
Submission Number / DP Barcode: ;
Decision No.:

PMRA Submission No.:
Active Ingredient: *S*-Abscisic acid
CANADA Common Name:

FROM: Sam Margerison, Senior Evaluator, Pesticide Residues Section, Pesticides Program, APVMA
TO:

1.3 Identity of the active ingredient

1.3.1 Name and address of the applicant

Australian street address	Australian contact and postal address
Valent Biosciences (a division of Sumitomo Chemical Australia) 501 Victoria Avenue Chatswood NSW 2067 Australia	Margot Davies Regulatory Officer Valent Biosciences (a division of Sumitomo Chemical Australia) PO Box 5125 Chatswood NSW 2067 Australia

US street address	US contact and postal address

Canadian street address	Canadian contact and postal address

1.3.2 Common name

There is no ISO-approved common name. 'Abscisic acid' has been in general scientific use as a name since 1968. The compound is enantiomeric, and the most biologically active enantiomer is the *S* form. This is the form which is proposed for registration. Hence the most appropriate common name is *S*-abscisic acid.

1.3.3 Chemical names

IUPAC name	(*S*)-(2*Z*,4*E*)-5-(1-Hydroxy-2,6,6-trimethyl-4-oxo-cyclohex-2-en-1-yl)-3-methylpenta-2,4-dienoic acid
Chemical abstracts name	(*S*)-5-(1-Hydroxy-2,6,6-trimethyl-4-oxo-2-cyclohexen-1-yl)-3-methyl-(2*Z*,4*E*)-pentadienoic acid

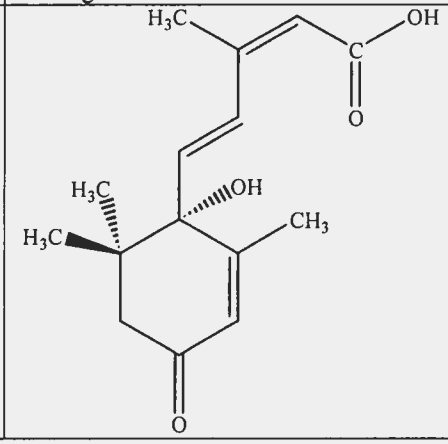
1.3.4 Manufacturer's number

VBC-30054.

1.3.5 Official identification numbers

CAS number:	21293-29-8
EINECS number:	Not provided/not available
CIPAC number:	Not provided/not available

1.3.6 Molecular formula and mass, structure

Molecular formula:	$C_{15}H_{20}O_4$
Molecular mass:	264.3 g/mol
Structure:	

1.3.7 Manufacturer of *S*-abscisic acid

Valent BioSciences Corporation

Address:
Lomon Biotechnology Co Ltd
325 Hexiang Road
Dayi County
Chengdu
Sichuan 611300
P.R. China

1.3.8 Method of manufacture of *S*-abscisic acid

See confidential appendix C for a detailed description of the manufacturing process for *S*-abscisic acid.

1.3.9 Specification for *S*-abscisic acid

Two specifications have been provided and are tabulated in confidential appendix C. The first was generated after analysis of a single batch of technical *S*-abscisic acid. The second was generated after five batches had been analysed.

The applicant will be required to clarify which is the specification that will apply to the technical S-abscisic acid.

1.3.10 Structures of *S*-abscisic acid impurities

Structure of the impurities found in technical *S*-abscisic acid are presented in the confidential appendix.

1.3.11 Analytical profile of batches of technical *S*-abscisic acid

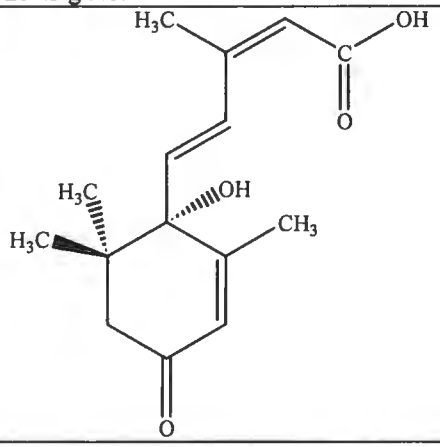
Results of analyses of five batches generated by a US laboratory (PTRL West Inc) for technical *S*-abscisic acid are presented in the confidential appendix. A single batch was analysed by the manufacturer Lomon Biotechnology Co Ltd. ***The applicant will be asked to comment on the differing impurity profiles for the single Lomon batch and the five batches tested by PTRL West.***

2. Statement of conclusions for *S*-abscisic acid technical active chemistry

2.1 Identity, physico-chemical properties, details of uses, further information, and proposed classification and labelling for S-abscisic acid

Active ingredient	*S*-Abscisic acid
Function	Plant growth regulator
Countries to which application is made	Australia, USA, Canada

2.1.1 Identity

IUPAC name	(*S*)-(2*Z*,4*E*)-5-(1-Hydroxy-2,6,6-trimethyl-4-oxo-cyclohex-2-en-1-yl)-3-methylpenta-2,4-dienoic acid
Chemical abstracts name	(*S*)-5-(1-Hydroxy-2,6,6-trimethyl-4-oxo-2-cyclohexen-1-yl)-3-methyl-(2*Z*,4*E*)-pentadienoic acid
CIPAC number	Not available
CAS number	21293-29-8
EINECS/ELINCS number	Not available
FAO specification	Not available
Minimum purity	950 g/kg
Relevant impurities	No impurities have been identified as being of environmental or toxicological significance
Molecular formula	$C_{15}H_{20}O_4$
Molecular mass	264.3 g/mol
Structure	

2.1.2 Physico-chemical properties of *S*-abscisic acid technical

Table 1: Physico-chemical properties of *S*-abscisic acid

Property	Value	Method reference
Melting point	Did not melt, decomposes	EEC method A.1 and A.2
Temperature of decomposition	159.2-162.2 °C (99.7% purity, 96.2% purity)	EEC method A.1 and A.2
Appearance and odour	White odourless powder (25 °C, 99.7% purity)	OPPTS Guidelines 830.630, 830.6302, and

		830.6304.
Density	1.21 g/cm^3 (96.2% purity)	OPPTS Guideline No. 830.7300.
Vapour pressure	<2 x 10^{-6} Pa (25 °C, 99.7% purity active) 5.8 x 10^{-7} Pa (calculated)	OPPTS Guideline No. 830.7950.
Henry's Law constant	4.8 x 10^{-8} Pa m^3/mol	Calculation from vapour pressure and water solubility.
Water solubility (99.7% purity active, 20 °C)	Distilled water: 3192 mg/L pH 4 buffer: 3102 mg/L	Shake flask method.
Solubility in organic solvents (99.7% purity active, 20 °C)	Methanol: 506.8 g/L Acetone: 290.2 g/L Ethyl acetate: 92.175 g/L 1,2-Dichloroethane: 10.95 g/L Xylene: 0.265 g/L Octanol: 54.8 g/L n-Heptane: 0.0057 g/L	OECD Guideline 105/OPPTS Guideline No. 830.7840
Octanol/water partition coefficient (99.7% purity active)	$\log_{10}P_{OW}$ (unionised form) = 1.8 $\log_{10}P_{OW}$ (unionised form) = 0.94	OPPTS Guideline No. 830.7570.
Hydrolysis (99.7% purity active,)	pH 4: k (25 °C) = -0.00088 days^{-1} (half life 792 days) pH 4: k (40 °C) = -0.0043 days^{-1} (half life 162 days) pH 7: very slow hydrolysis pH 9: very slow hydrolysis	OECD Guideline No. 111 and OPPTS Guideline No. 835.2110.
Dissociation constant	pK_a = 4.61 (99.7% purity active)	Titration with 0.1M NaOH
pH of solution	3.32 (1% aqueous solution/suspension of 96.2% purity active)	OPPTS Guideline No. 830.7000.
Specific rotation	409.97° (in ethanol, 10.1 mg/mL, 20 °C)	
Flammability	Not highly flammable (97.0% purity active)	EEC method A10
Explosive properties	Not heat, friction or shock sensitive (97.0% purity active)	EEC method A14
Self-ignition temperature	No self heating below 400 °C (97.0% purity active)	EEC method A16
Accelerated storage stability	No significant degradation on storage at 54 °C for 14 days (97.0% purity active)	OPPTS Guideline No. 830.6313
Oxidative/reductive stability	Oxidised by 5% potassium permanganate solution, which was converted to manganese dioxide. No changes observed with zinc metal, carbon dioxide or water. (97.0% purity active)	OPPTS Guideline No. 830.6314
Stability in the presence of metals and metal ions	No significant degradation over 14 days at 54 °C when stored in the presence of aluminium shot, iron shot, aluminium acetate or iron(II) acetate. (97.0% purity active)	OPPTS Guideline No. 830.6313

The physico-chemical properties were determined using suitable test methods, in accordance with the OECD Principles of Good Laboratory Practice (GLP).

Normal and accelerated temperature stability of technical *S*-abscisic acid was tested by placing approximately 5 grams of sample in a glass tube capped with an amber glass vial filled with lead shot to maintain pressure on the sample. The sample was stored in a dry oven at 55 ± 2 °C (accelerated storage) or in an amber glass bottle to shield from light at room temperature (ambient storage). 500 mg aliquots were stored in the presence of 1 gram of aluminium or iron shot, or aluminium or iron(II) acetate in a glass vial at 54 °C for the metal/metal ion stability testing. Samples were tested after 0, 1, 2, 7 and 14 days storage. A suitable validated reverse phase isocratic HPLC-UV (262 nm) method was

used to analyse the samples before and after storage for *S*-abscisic acid content. Oxidative and reductive properties of *S*-abscisic acid were tested by storing and observing samples of the technical material in a glass tube in the presence of water, carbon dioxide, 5% potassium permanganate solution, or zinc over 24 hours at 21-22 °C. This study was conducted in accordance with the OECD Principles of Good Laboratory Practice (GLP). The study report was acceptable.

A reference standard of *S*-abscisic acid (purity) was analysed by ^{1}H and ^{13}C NMR together with some more advanced NMR techniques, infrared and ultraviolet spectroscopy, mass spectrometry, optical rotary dispersion, Karl Fischer titration for determination of water content, residue on ignition, and HPLC-UV for determination of purity.

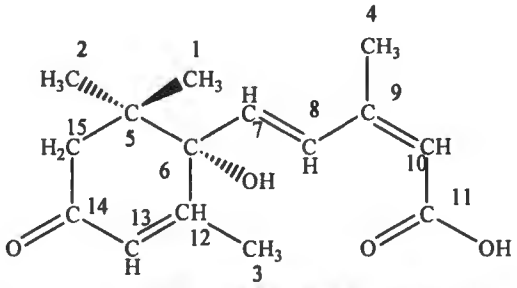


Figure: *S*-Abscisic acid labelled for the purposed of ^{1}H and ^{13}C NMR spectral assignment

Table 2: Assignment of ^{1}H and ^{13}C NMR resonances

Assignment	^{1}H NMR resonance (ppm)	^{13}C NMR resonance (ppm)
1 or 2	0.94 (s, 3H)	23.20
1 or 2	0.97 (s, 3H)	24.18
3	1.84 (d, 3H)	18.86
4	1.99 (s, 3H)	20.85
5	-	41.27
6	-	78.39
7	6.25 (d, 1H)	137.38
8	7.76 (d, 1H)	127.30
9	-	141.19
10	5.68 (s, 1H)	118.41
11	-	166.89
12	-	163.14
13	5.82 (s, 1H)	125.94
14	-	197.18
15	2.14 (d, 1H), 2.55 (d, 1H)	49.36
Acid OH	12.05 (bs, 1H)	-
Alcohol OH	5.20 (bs, 1H)	-

The above assignments were determined with the assistance of two dimensional NMR techniques such as COSY, DEPT, HETCOR and HMBC.

The infrared spectrum of the *S*-abscisic acid reference standard was consistent with the structure and showed characteristic peaks between 1700 and 1640 cm^{-1}, which are due to the αβ-unsaturated ketone and αβ-unsaturated acid C=O stretch, peaks between 1590 and 1640 cm^{-1}, which are probably due to C=C stretches, a strong broad peak at 3414 cm^{-1} due to the O-H stretch, between 1400 and 1300 cm^{-1} and between 1200 and 1100 cm^{-1} due to the coupled C-O alcohol stretch and O-H alcohol deformation, and between 1300 and 1200 cm^{-1} due to C-O acid stretching.

The mass spectrum showed a strong molecular ion peak at m/z = 263.2. Fragment ion peaks at m/z = 219.3 and 153.0 were due to elimination of a CO_2 fragment and loss of the entire pentadienoic acid side chain respectively. ***The origin of the higher mass peaks at 331.3, 527.7, 549.5, 617.6, 813.8, 835.9 and 903.7 is not clear and the applicant will be asked to comment.***

A UV/visible absorption spectrum of a 2 mg/mL solution in ethanol was measured over the range 200-800 nm in the first report. A strong absorption peak centred around 240 nm was observed. The solution appears to have been too concentrated, as the peak absorbance was very high (>3), resulting in low signal and a poor signal to noise ratio at the absorbance maximum. A 2-3 fold dilution of the solution used would have been a better choice. The second report on spectroscopic analysis of the reference standard included a re-run of the UV/visible spectrum using a more dilute solution (0.000038 $molL^{-1}$ instead of 0.0076 $molL^{-1}$). This gave a spectrum with a much better signal to noise ratio, and an absorption maximum at 258 nm with a molar absorptivity of 21789 $Lmol^{-1}cm^{-1}$.

Water content of the *S*-abscisic acid reference standard was determined by Karl Fischer titration to be <0.048% (<0.48 g/kg). Residue on ignition was determined to be <0.10%.

HPLC analysis for active constituent purity was conducted using an isocratic reverse phase HPLC-UV (262 nm) method that was similar to those used for the analyses in other physico-chemical property studies (e.g. water solubility, storage stability, vapour pressure). Total impurities detectable by HPLC were [redacted] The purity of the material was calculated as 99.7% by subtraction of the total HPLC impurities and residue on ignition. ***The applicant will be asked to comment on whether an analysis of the S-abscisic acid content of the reference standard was conducted using a primary analytical method.***

S-Abscisic acid is strongly optically active, with a 10.1 mg/mL ethanol solution showing a specific rotation for 589 nm light at 20 °C of 409.97°.

The spectroscopic and chromatographic analyses of *S*-abscisic acid for the purposes of designating a reference standard were conducted in accordance with the OECD Principles of Good Laboratory Practice (GLP). The reports are acceptable.

S-Absisic acid is an essentially non-volatile white odourless solid, slightly soluble in water, highly soluble in polar organic solvents, slightly soluble in aromatic non-polar organic solvents and essentially insoluble in aliphatic non-polar solvents. It has a $\log_{10}P_{OW}$ value of 1.8 and 0.94 in the unionised and ionised forms respectively and as a result is not likely to be fat soluble or to bio-accumulate. It decomposes with melting at 159.2-162.2 °C. As its name suggests, it is a weak acid with a pK_a of 4.61. No hydrolysis was observed in preliminary experiments over 5 days at 50 °C at pH 7 and 9. Very slow hydrolysis (half life > 2 years) was observed in pH 4 buffer at 25 °C, with more rapid degradation (half life of 162 days) in pH 4 buffer at 40 °C. *S*-Abscisic acid demonstrates excellent safety properties, as it is not highly flammable, is not heat, friction or shock sensitive and does not undergo self-ignition. It is stable under accelerated storage conditions (14 days at 54 °C), with or without the presence of metals (aluminium or iron shot) or metal ions (aluminium acetate or iron(II) acetate). It is not reduced by zinc metal, but is oxidised by potassium permanganate (a 5% solution). Manganese dioxide is formed as a by-product.

2.2 Methods of analysis

2.2.1 Analytical methods for analysis of the active ingredient as manufactured

a) Brief method details

A reverse-phase isocratic HPLC-UV method was employed to quantify the *S*-abscisic acid content of the technical active ingredient. Quantification was achieved by linear regression external standard calibration (99.7% purity reference standard). Sample raw data allowed calculations to be reproduced.

b) Conclusion

The analytical method has been appropriately validated for analysis of *S*-abscisic acid, demonstrates excellent linearity, precision and accuracy and shows no evidence of any co-eluting interferents. It is therefore suitable for the determination of the purity of technical *S*-abscisic acid.

3. Proposed decision with respect to the chemistry aspects of *S*-abscisic acid technical active ingredient

Approval/registration of the new active constituent *S*-abscisic acid is supported from a chemistry perspective, pending an acceptable response to the points listed at section 4 below.

4. Further information to permit a decision to be made

- ***The applicant will be required to clarify which is the specification that will apply to the technical S-abscisic acid.***
- ***The applicant will be asked to comment on the differing impurity profiles for the single Lomon batch and the five batches tested by PTRL West.***
- ***The origin of the higher mass peaks at 331.3, 527.7, 549.5, 617.6, 813.8, 835.9 and 903.7 in the mass spectra of S-abscisic acid is not clear and the applicant will be asked to comment.***
- ***The applicant will be asked to comment on whether an analysis of the S-abscisic acid content of the reference standard was conducted using a primary analytical method.***
- [redacted]
- ***Further details may be required for the Lomon analytical methods if the batch analysis from Lomon Biotechnology is to be relied upon.***
- ***Currently, the HPLC methods for determination of the active constituent purity do not provide any confirmation of the stereochemistry of abscisic acid, as the methods do not use a chiral column and will not separate the two enantiomers. The measurement of the specific optical rotation of S-abscisic acid is acknowledged, however this measurement only appears to have been conducted for a batch of the material used as a reference standard (99.7% purity). The applicant will be required to provide some analyses of batches of the technical active constituent to confirm the optical purity i.e. the proportions of the S and R enantiomers.***

Manufacturing process information may be entitled to confidential treatment

A. List of chemistry tests and studies submitted in respect of technical *S*-abscisic acid

Author(s)	OECD data point number/ reference number	Year	Title Source (where different from applicant) Company, report no. GLP status Published or not	Data protection eligible (Y/N)	Owner
Ponte, M	IIA 2.3.1	2006	Vapour Pressure of S-Abscisic Acid PTRL Report No. 1436W-1 GLP, Unpublished	Y	Valent
Ponte, M	Not known	2006	Physical Properties: pH Determination of S-Abscisic Acid Technical Grade Active Ingredient in Water PTRL Project No. 1558W GLP, Unpublished	Y	Valent
Ponte, M	IIA 2.6, IIA 2.8, IIA 2.10	2006	S-Abscisic Acid: Dissociation Constant in Water, Water Solubility and n-Octanol/water Partition Coefficient PTRL West Project No. 1437W GLP, Unpublished	Y	Valent
Ponte, M	IIA 2.1.1, IIA 2.1.3, IIA 2.2, IIA 2.4.1, IIA 2.4.2	2005	Physical Properties of S-Abscisic Acid Technical Grade Active Ingredient PTRL West Project No. 1438W GLP, Unpublished	Y	Valent
Schick, M	IIA 2.7	2008	Solubility of S-Abscisic Acid in Organic Solvents PTRL West Report No. 1730W-1 GLP, Unpublished	Y	Valent
Schick, M	IIA 2.9.1	2008	Hydrolysis of S-Abscisic Acid at pH 4, 7 and 9 PTRL West Report No. 1729W-1 GLP, Unpublished	Y	Valent
Comb, A.L.	IIA 2.11.1, IIA 2.11.2, IIA 2.13, IIA 2.15	2007	VBC-30054 Physico-chemical Properties Huntingdon Life Sciences project no. ZAB/0083 GLP, Unpublished	Y	Valent
Bade, T.	IIA 2	2006	Summary of Physical Chemistry Properties of S-Abscisic Acid: VBC-30054 Technical Material Laboratory Project ID: S-ABA 30054; 056-3	N	Valent

			Not GLP, Unpublished		
Ponte, M.	Not known	2007	Stability of S-Abscisic Acid Active Ingredient Relative to Normal and Elevated Temperatures, Metals and Metal Ions, and Oxidising and Reducing Properties of S-Abscisic Acid Active Ingredient PTRL West Report No. 1618W-1 GLP, Unpublished	Y	Valent
Zhang, H.	IIA 2.5.1	2004	Certification of S-ABA Reference Standard (Lot # 030806D1) Report No. REP-RC-2004-048 GLP, Unpublished	Y	Valent
Zhang, H.	IIA 2.5.1	2005	Retest of S-ABA Reference Standard (Lot # 030806D1) Report No. REP-RC-2005-039 GLP, Unpublished	Y	Valent
Rose, J.E.	IIA 1.11	2007	Analysis and Certification of Product Ingredients in Five Batches of Technical S-Abscisic Acid PTRL Study No. 1473W GLP, Unpublished	Y	Valent
Rose, J.E.	IIA 4.1? IIA 4.2?	2006	Method Validation for the Analysis of S-Abscisic Acid in Reference Standard, Technical Grade Active Ingredient and Formulated Products PTRL Study No. 1442W GLP, Unpublished	Y	Valent
Baldi, B.	IIA 4.1? IIA 4.2?	2005	Analytical Method for the Determination of *S*-Abscisic Acid (S-ABA) by High Performance Liquid Chromatography Method No. VBC-M04001 2 Not GLP, Unpublished	N	Valent
Bade, T.	IIA 1.8	2007	Integrated Manufacturing Process S-ABA (S-Abscisic Acid) Project ID: S-ABA 30054 027-1 Not GLP, Unpublished	Y	Valent
Bade, T.	IIA 1.11	2008	S-Abscisic Acid: VBC-30054 Technical Powder Product Chemistry: Certification of Limits Project ID: S-ABA 30054 127-2 Not GLP, Unpublished	N	Valent
Baldi, B.	IIA 4.1? IIA 4.2?	2007	Characterisation of the 1',4'-*trans*-diol of abscisic acid reference substance (VBC-30084) Study number: VBCL07-48060-01 GLP, Unpublished	Y	Valent

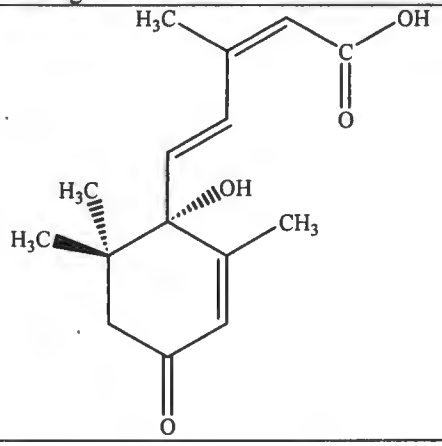
Bade, T.	IIA 1.11	2007	S-Abscisic Acid: VBC-30054 Technical Powder Product Chemistry: Analysis, Certification of Limits, Analytical Methods Laboratory Project ID: S-ABA 30054, 027-2 Not GLP, Unpublished	Y	Valent

B. Summary, evaluation and assessment of the chemistry data and information for technical *S*-abscisic acid

B.1 Identity

Active ingredient	*S*-Abscisic acid
Function	Plant growth regulator
Countries to which application is made	Australia, USA, Canada

B.1.1 Identity of the active ingredient

IUPAC name	(*S*)-(2*Z*,4*E*)-5-(1-Hydroxy-2,6,6-trimethyl-4-oxo-cyclohex-2-en-1-yl)-3-methylpenta-2,4-dienoic acid
Chemical abstracts name	(*S*)-5-(1-Hydroxy-2,6,6-trimethyl-4-oxo-2-cyclohexen-1-yl)-3-methyl-(2*Z*,4*E*)-pentadienoic acid
CIPAC number	Not available
CAS number	21293-29-8
EINECS/ELINCS number	Not available
FAO specification	Not available
Minimum purity	950 g/kg
Relevant impurities	No impurities have been identified as being of environmental or toxicological significance
Molecular formula	$C_{15}H_{20}O_4$
Molecular mass	264.3 g/mol
Structure	

B.1.2 References relied on

Not applicable.

B.2 Physico-chemical properties

B.2.1 Physico-chemical properties of *S*-abscisic acid technical

Table 3: Physico-chemical properties of *S*-abscisic acid

Property	Value	Method reference
Melting point	Did not melt, decomposes	EEC method A.1 and A.2
Temperature of	159.2-162.2 °C (99.7% purity, 96.2%	EEC method A.1 and A.2

decomposition	purity)	
Appearance and odour	White odourless powder (25 °C, 99.7% purity)	OPPTS Guidelines 830.630, 830.6302, and 830.6304.
Density	1.21 g/cm^3 (96.2% purity)	OPPTS Guideline No. 830.7300.
Vapour pressure	<2 x 10^{-6} Pa (25 °C, 99.7% purity active) 5.8 x 10^{-7} Pa (calculated)	OPPTS Guideline No. 830.7950.
Henry's Law constant	4.8 x 10^{-8} Pa m^3/mol	Calculation from vapour pressure and water solubility.
Water solubility (99.7% purity active, 20 °C)	Distilled water: 3192 mg/L pH 4 buffer: 3102 mg/L	Shake flask method.
Solubility in organic solvents (99.7% purity active, 20 °C)	Methanol: 506.8 g/L Acetone: 290.2 g/L Ethyl acetate: 92.175 g/L 1,2-Dichloroethane: 10.95 g/L Xylene: 0.265 g/L Octanol: 54.8 g/L n-Heptane: 0.0057 g/L	OECD Guideline 105/OPPTS Guideline No. 830.7840
Octanol/water partition coefficient (99.7% purity active)	$\log_{10}P_{OW}$ (unionised form) = 1.8 $\log_{10}P_{OW}$ (unionised form) = 0.94	OPPTS Guideline No. 830.7570.
Hydrolysis (99.7% purity active,)	pH 4: k (25 °C) = -0.00088 days^{-1} (half life 792 days) pH 4: k (40 °C) = -0.0043 days^{-1} (half life 162 days) pH 7: very slow hydrolysis pH 9: very slow hydrolysis	OECD Guideline No. 111 and OPPTS Guideline No. 835.2110.
Dissociation constant	pK_a = 4.61 (99.7% purity active)	Titration with 0.1M NaOH
pH of solution	3.32 (1% aqueous solution/suspension of 96.2% purity active)	OPPTS Guideline No. 830.7000.
Specific rotation	409.97° (in ethanol, 10.1 mg/mL, 20 °C)	
Flammability	Not highly flammable (97.0% purity active)	EEC method A10
Explosive properties	Not heat, friction or shock sensitive (97.0% purity active)	EEC method A14
Self-ignition temperature	No self heating below 400 °C (97.0% purity active)	EEC method A16
Accelerated storage stability	No significant degradation on storage at 54 °C for 14 days (97.0% purity active)	OPPTS Guideline No. 830.6313
Oxidative/reductive stability	Oxidised by 5% potassium permanganate solution, which was converted to manganese dioxide. No changes observed with zinc metal, carbon dioxide or water. (97.0% purity active)	OPPTS Guideline No. 830.6314
Stability in the presence of metals and metal ions	No significant degradation over 14 days at 54 °C when stored in the presence of aluminium shot, iron shot, aluminium acetate or iron(II) acetate. (97.0% purity active)	OPPTS Guideline No. 830.6313

No *S*-abscisic acid was detected in the traps of the gas saturation apparatus used to determine the vapour pressure. The method limit of quantitation equated to 1.2 µg per trap, hence the vapour pressure at 25 °C was estimated to be <2 x 10^{-6} Pa. A second figure of 5.8 x 10^{-7} Pa was calculated using the MPBPWIN program from the EPI suite 3.1 software. The Henry's Law constant was calculated as part of this study from the vapour pressure and the water solubility. A suitable validated reverse-phase isocratic HPLC-UV (262 nm) method was used to analyse the trapped material for *S*-

abscisic acid. The study was conducted in accordance with the OECD Principles of Good Laboratory Practice (GLP). The study report was acceptable.

The pH of a stirred 1% slurry of *S*-abscisic acid in deionised water was determined using a pH meter. The pH study was conducted in accordance with the OECD Principles of Good Laboratory Practice (GLP). The study report was acceptable.

Water solubility, pK_a and $\log_{10}P_{OW}$ were determined as part of a single study using the shake flask method, titration with 0.1M sodium hydroxide solution with plotting of pH vs volume of base added, and by the HPLC method , respectively. Solubility was determined by the shake flask method in freshly distilled deionised water and in pH 4 acetate/acetic acid buffer. A suitable validated reverse phase isocratic HPLC-UV (262 nm) method was used to determine the *S*-abscisic acid content of the supernatant for the solubility measurement. For the determination of the octanol/water partition coefficient, a series of reference standards with well-known $\log_{10}P_{OW}$ values were chosen (phenoxyacetic acid, benzoic acid, 4-chlorophenol, toluene, bromobenzene and naphthalene for the acidic solution, i.e. the unionised form, and toluene, bromobenzene, naphthalene, butanone and benzene for the neutral solution, i.e. the ionised form). The same HPLC instrument and column were used for the neutral and acidic analyses, the only difference was the mobile phases, which were 3:1 methanol/water (pH 6.2) and 3:1 methanol/0.1% trifluoroacetic acid (pH 2.5) respectively. A solution of the appropriate series of reference standards was analysed using the respective HPLC method, together with a solution of *S*- abscisic acid in acidic mobile phase (i.e. at pH 2.5) for the acidic method, and a solution of *S*-abscisic acid in acidic mobile phase, with sufficient 1M sodium hydroxide to raise the pH to 10 for the neutral method. The dead time (i.e. void volume) for the analysis was determined by running a sample of acetone in methanol/0.1% TFA using methanol only as the mobile phase to ensure no retention. The capacity factor (k') was calculated for each standard ($k' = (t_R - t_0)/t_0$, where t_R = retention time, and t_0 = dead time) and all $\log_{10}k'$ values were plotted against their corresponding $\log_{10}P_{OW}$ values. The $\log_{10}P_{OW}$ for *S*-abscisic acid was then determined by interpolation of its $\log_{10}k'$ value. This study was conducted in accordance with the OECD Principles of Good Laboratory Practice (GLP). The study report was acceptable.

Density was determined using a pycnometer. Appearance and odour were determined by visual and olfactory inspection after equilibration of the sample at 25 °C. The melting/decomposition temperature was determined using the capillary method. This study was conducted in accordance with the OECD Principles of Good Laboratory Practice (GLP). The study report was acceptable.

Solubility in a range of organic solvents was determined by the shaken flask method. A suitable reverse phase isocratic HPLC-UV (262 nm) method was used to analyse the solutions for *S*-abscisic acid content. This study was conducted in accordance with the OECD Principles of Good Laboratory Practice (GLP). The study report was acceptable.

Preliminary experiments for determination of the rate of hydrolysis of *S*-abscisic acid were conducted in sterile aqueous buffers at pH 4, 7 and 9. A more definitive experiment was conducted at pH 4. A suitable reverse phase isocratic HPLC-UV (262 nm) method was used to analyse the aqueous solutions for *S*-abscisic acid content. This study was conducted in accordance with the OECD Principles of Good Laboratory Practice (GLP). The study report was acceptable.

S-Absisic acid is an essentially non-volatile white odourless solid, slightly soluble in water, highly soluble in polar organic solvents, slightly soluble in aromatic non-polar organic solvents and essentially insoluble in aliphatic non-polar solvents. It has a $\log_{10}P_{OW}$ value of 1.8 and 0.94 in the unionised and ionised forms respectively and as a result is not likely to be fat soluble or to bio-accumulate. It decomposes with melting at 159.2-162.2 °C. As its name suggests, it is a weak acid with a pK_a of 4.61. No hydrolysis was observed in preliminary experiments over 5 days at 50 °C at pH 7 and 9. Very slow hydrolysis (half life > 2 years) was observed in pH 4 buffer at 25 °C, with more rapid degradation (half life of 162 days) in pH 4 buffer at 40 °C.

B.2.2 Stability and safety properties of technical *S*-abscisic acid

Normal and accelerated temperature stability of technical *S*-abscisic acid was tested by placing approximately 5 grams of sample in a glass tube capped with an amber glass vial filled with lead shot to maintain pressure on the sample. The sample was stored in a dry oven at 55 ± 2 °C (accelerated

storage) or in an amber glass bottle to shield from light at room temperature (ambient storage). 500 mg aliquots were stored in the presence of 1 gram of aluminium or iron shot, or aluminium or iron(II) acetate in a glass vial at 54 °C for the metal/metal ion stability testing. Samples were tested after 0, 1, 2, 7 and 14 days storage. A suitable validated reverse phase isocratic HPLC-UV (262 nm) method was used to analyse the samples before and after storage for *S*-abscisic acid content. Oxidative and reductive properties of *S*-abscisic acid were tested by storing and observing samples of the technical material in a glass tube in the presence of water, carbon dioxide, 5% potassium permanganate solution, or zinc over 24 hours at 21-22 °C. This study was conducted in accordance with the OECD Principles of Good Laboratory Practice (GLP). The study report was acceptable.

Flammability was tested using a pile of packed solid of triangular cross-section of 20 mm base width, 10 mm height and 250 mm length. A gas burner was used to apply a flame to one end. A substance is deemed highly flammable if having burned for a length of 80 mm, it burns a length of 100 mm in less than 45 seconds. The material melted and burnt with a yellow flame, but extinguished within 2 seconds of removing the heat source and the flame did not propagate along the pile. Hence it was not classified as highly flammable. Shock testing was conducted using the hammer and anvil method. Friction testing was conducted by drawing a porcelain peg with a loading of 360 N back and forth across a 10 mm^3 pile on a porcelain plate. Heat sensitivity was tested by heating steel tubes containing the sample in a propane gas flame. Self-ignition was tested by heating a sample of the material in a furnace at 0.5 °C/min to 400 °C and monitoring the sample and furnace temperatures. This study was conducted in accordance with the OECD Principles of Good Laboratory Practice (GLP). The study report was acceptable.

Technical *S*-abscisic acid is stable under accelerated storage conditions (14 days at 54 °C), with or without the presence of metals (aluminium or iron shot) or metal ions (aluminium acetate or iron(II) acetate). *S*-Abscisic acid demonstrates excellent safety properties, as it is not highly flammable, is not heat, friction or shock sensitive and does not undergo self-ignition. It is not reduced by zinc metal, but is oxidised by potassium permanganate (a 5% solution). Manganese dioxide is formed as a by-product.

B.2.3 Spectroscopy of *S*-abscisic acid

A reference standard of *S*-abscisic acid (purity) was analysed by ^{1}H and ^{13}C NMR together with some more advanced NMR techniques, infrared and ultraviolet spectroscopy, mass spectrometry, optical rotary dispersion, Karl Fischer titration for determination of water content, residue on ignition, and HPLC-UV for determination of purity.

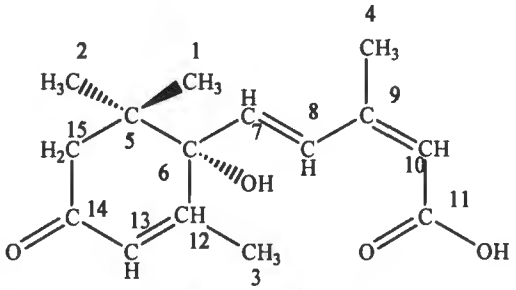


Figure: *S*-Abscisic acid labelled for the purposed of ^{1}H and ^{13}C NMR spectral assignment

Table 4: Assignment of ^{1}H and ^{13}C NMR resonances

Assignment	^{1}H NMR resonance (ppm)	^{13}C NMR resonance (ppm)
1 or 2	0.94 (s, 3H)	23.20
1 or 2	0.97 (s, 3H)	24.18
3	1.84 (d, 3H)	18.86
4	1.99 (s, 3H)	20.85
5	-	41.27
6	-	78.39
7	6.25 (d, 1H)	137.38
8	7.76 (d, 1H)	127.30
9	-	141.19
10	5.68 (s, 1H)	118.41

11	-	166.89
12	-	163.14
13	5.82 (s, 1H)	125.94
14	-	197.18
15	2.14 (d, 1H), 2.55 (d, 1H)	49.36
Acid OH	12.05 (bs, 1H)	-
Alcohol OH	5.20 (bs, 1H)	-

The above assignments were determined with the assistance of two dimensional NMR techniques such as COSY, DEPT, HETCOR and HMBC.

The infrared spectrum of the *S*-abscisic acid reference standard was consistent with the structure and showed characteristic peaks between 1700 and 1640 cm^{-1}, which are due to the αβ-unsaturated ketone and αβ-unsaturated acid C=O stretch, peaks between 1590 and 1640 cm^{-1}, which are probably due to C=C stretches, a strong broad peak at 3414 cm^{-1} due to the O-H stretch, between 1400 and 1300 cm^{-1} and between 1200 and 1100 cm^{-1} due to the coupled C-O alcohol stretch and O-H alcohol deformation, and between 1300 and 1200 cm^{-1} due to C-O acid stretching.

The mass spectrum showed a strong molecular ion peak at m/z = 263.2. Fragment ion peaks at m/z = 219.3 and 153.0 were due to elimination of a CO_2 fragment and loss of the entire pentadienoic acid side chain respectively. ***The origin of the higher mass peaks at 331.3, 527.7, 549.5, 617.6, 813.8, 835.9 and 903.7 is not clear and the applicant will be asked to comment.***

A UV/visible absorption spectrum of a 2 mg/mL solution in ethanol was measured over the range 200-800 nm in the first report. A strong absorption peak centred around 240 nm was observed. The solution appears to have been too concentrated, as the peak absorbance was very high (>3), resulting in low signal and a poor signal to noise ratio at the absorbance maximum. A 2-3 fold dilution of the solution used would have been a better choice. The second report on spectroscopic analysis of the reference standard included a re-run of the UV/visible spectrum using a more dilute solution (0.000038 $molL^{-1}$ instead of 0.0076 $molL^{-1}$). This gave a spectrum with a much better signal to noise ratio, and an absorption maximum at 258 nm with a molar absorptivity of 21789 $Lmol^{-1}cm^{-1}$.

Water content of the *S*-abscisic acid reference standard was determined by Karl Fischer titration to be <0.048% (<0.48 g/kg). Residue on ignition was determined to be <0.10%.

HPLC analysis for active constituent purity was conducted using an isocratic reverse phase HPLC-UV (262 nm) method that was similar to those used for the analyses in other physico-chemical property studies (e.g. water solubility, storage stability, vapour pressure). Total impurities detectable by HPLC were [redacted]. The purity of the material was calculated as 99.7% by subtraction of the total HPLC impurities and residue on ignition. ***The applicant will be asked to comment on whether an analysis of the S-abscisic acid content was conducted.***

S-Abscisic acid is strongly optically active, with a 10.1 mg/mL ethanol solution showing a specific rotation for 589 nm light at 20 °C of 409.97°.

The spectroscopic and chromatographic analyses of *S*-abscisic acid for the purposes of designating a reference standard were conducted in accordance with the OECD Principles of Good Laboratory Practice (GLP). The reports are acceptable.

B.2.4 References relied on

Table 5: References relied on in respect of physico-chemical, stability, safety and spectroscopic properties

Author(s)	Year	Title Source (where different from applicant) Company, report no. GLP status Published or not
Ponte, M	2006	Vapour Pressure of S-Abscisic Acid

		PTRL Report No. 1436W-1 GLP, Unpublished
Ponte, M	2006	Physical Properties: pH Determination of S-Abscisic Acid Technical Grade Active Ingredient in Water PTRL Project No. 1558W GLP, Unpublished
Ponte, M	2006	S-Abscisic Acid: Dissociation Constant in Water, Water Solubility and n-Octanol/water Partition Coefficient PTRL West Project No. 1437W GLP, Unpublished
Ponte, M	2005	Physical Properties of S-Abscisic Acid Technical Grade Active Ingredient PTRL West Project No. 1438W GLP, Unpublished
Schick, M	2008	Solubility of S-Abscisic Acid in Organic Solvents PTRL West Report No. 1730W-1 GLP, Unpublished
Schick, M	2008	Hydrolysis of S-Abscisic Acid at pH 4, 7 and 9 PTRL West Report No. 1729W-1 GLP, Unpublished
Comb, A.L.	2007	VBC-30054 Physico-chemical Properties Huntingdon Life Sciences project no. ZAB/0083 GLP, Unpublished
Bade, T.	2006	Summary of Physical Chemistry Properties of S-Abscisic Acid: VBC-30054 Technical Material Laboratory Project ID: S-ABA 30054; 056-3 Not GLP, Unpublished
Ponte, M.	2007	Stability of S-Abscisic Acid Active Ingredient Relative to Normal and Elevated Temperatures, Metals and Metal Ions, and Oxidising and Reducing Properties of S-Abscisic Acid Active Ingredient PTRL West Report No. 1618W-1 GLP, Unpublished
Zhang, H.	2004	Certification of S-ABA Reference Standard (Lot # 030806D1) Report No. REP-RC-2004-048 GLP, Unpublished
Zhang, H.	2005	Retest of S-ABA Reference Standard (Lot # 030806D1) Report No. REP-RC-2005-039 GLP, Unpublished

B.3 Methods of analysis

B.3.1 Analytical methods for analysis of the active ingredient as manufactured

a) Method details

A reverse-phase isocratic HPLC-UV method was employed to quantify the *S*-abscisic acid content of the technical active ingredient. Quantification was achieved by linear regression external standard calibration (99.7% purity reference standard). Sample raw data allowed calculations to be reproduced. Key instrumental parameters are tabulated below.

Table 6: Instrumental parameters for analysis of *S*-abscisic acid content of the technical active ingredient

Parameter	Value
Instrument	Agilent 1100 LC pump, with Agilent series UV/VIS diode array detector, Chem Station integrator, Agilent 1100 column heater, and Agilent 1100 autosampler.
Column	Zorbax ODS (150 x 3.0 mm x 5 µm) with C18 guard column (100 x 4.3 mm internal diameter)
Column temperature	30 °C

Mobile phase	10 mM K_2HPO_4 (pH adjusted to 3.0 with H_3PO_4): acetonitrile: tetrahydrofuran (75:23:2 v/v/v)
Detection wavelength	262 nm
Injection volume	50 µL
Flow rate	1 mL/min
Injector wash	Acetonitrile/water (25:75)

Representative examples of blank, sample and standard chromatograms were provided showing *S*-abscisic acid to elute reproducibly at 3.8 minutes, with well-shaped peaks. There were no co-eluting interferents.

b) Validation data

The method was validated and the validation data supplied with the first report is shown in the table below.

Table 7: Method validation for determination of purity of *S*-abscisic acid technical active ingredient

Parameter	Value
Linearity	r^2 = 1.0000 (0.5-20 mg/L in solution, corresponding to 10-400% of the typical sample solution concentration)
Precision	RSD = 0.28% (n = 9)
Accuracy	Recovery = 99.6-100.6% (n = 6)
Limit of detection/ quantitation	LOD = 0.003 µg/mL, corresponding to a 0.06 mg sample LOQ = 0.01 µg/mL, corresponding to a 0.2 mg sample

c) GLP status

This study was conducted in full compliance with the OECD Principles of Good Laboratory Practice (GLP) under the US Federal Insecticide, Fungicide and Rodenticide Act (FIFRA, 40 CFR, Part 160).

d) Conclusion

The analytical method has been appropriately validated for analysis of *S*-abscisic acid, demonstrates excellent linearity, precision and accuracy and shows no evidence of any co-eluting interferents. It is therefore suitable for the determination of the purity of technical *S*-abscisic acid.

B.3.2 Analytical methods for determination of impurities in technical *S*-abscisic acid

These methods are described in sections C.1.5 and C.1.6 of confidential appendix C.

B.3.3 References relied on

Table 8: References relied on in respect of analytical methods

Author(s)	Year	Title Source (where different from applicant) Company, report no. GLP status Published or not
Rose, J.E.	2007	Analysis and Certification of Product Ingredients in Five Batches of Technical S-Abscisic Acid PTRL Study No. 1473W GLP, Unpublished
Rose, J.E.	2006	Method Validation for the Analysis of S-Abscisic Acid in Reference Standard, Technical Grade Active Ingredient and Formulated Products PTRL Study No. 1442W GLP, Unpublished
Baldi, B.	2005	Analytical Method for the Determination of *S*-Abscisic Acid (S-ABA) by High Performance Liquid Chromatography Method No. VBC-M04001 2 Not GLP, Unpublished
Bade, T.	2008	S-Abscisic Acid: VBC-30054 Technical Powder Product Chemistry:

		Certification of Limits Project ID: S-ABA 30054 127-2 Not GLP, Unpublished
Baldi, B.	2007	Characterisation of the 1',4'-*trans*-diol of abscisic acid reference substance (VBC-30084) Study number: VBCL07-48060-01 GLP, Unpublished
Bade, T.	2007	S-Abscisic Acid: VBC-30054 Technical Powder Product Chemistry: Analysis, Certification of Limits, Analytical Methods Laboratory Project ID: S-ABA 30054, 027-2 Not GLP, Unpublished

C. Confidential appendix

C.1 Confidential information

C.1.1 Method of manufacture

[redacted]

[redacted]

Manufacturing process information may be entitled to confidential treatment

474704-00

474705-00

VALENT BIOSCIENCES™
CORPORATION

870 TECHNOLOGY WAY
LIBERTYVILLE, IL 60048 - 800-323-9597

July 7, 2008

Ms Janet Anderson
Document Processing Desk
Office of Pesticide Programs (7504C)
U.S. Environmental Protection Agency
Room 266A, Crystal Mall 2
1921 Jefferson Davis Highway
Arlington, VA 22202

Attention: Mr. Chris Pfiefer
Regulatory Action Leader
Biochemical Pesticides Branch
Biopesticides and Pollution Prevention Division (7511P)
U.S. Environmental Protection Agency

Subject: Valent BioSciences Corp.
EPA Reg. No. 73049-XX,
Request for the Registration of S-Abscisic Acid (VBC-30054, TGAI), and
Two End Use Formulations (VBC-30051 & VBC-30101),
for use on Ornamental and Grape crops.

Dear Ms. Anderson,

The following pesticide registration application for the biochemical plant growth regulator S-Abscisic Acid (S-ABA) is submitted by Valent BioSciences Corp. for your consideration.

This is in continuation of many interactions and submissions presented to the United State Environmental Protection Agency (EPA). A pre-registration conference was held between Valent BioSciences and EPA on July 13, 2005. An Experimental Use Permit for use of S-ABA on Ornamentals for stress reduction (# 73049-EUP-3) was issued on February 15, 2007. This Experimental Use Permit (#72049-EUP-3) originally restricted the use to within greenhouses only. This restriction was removed on December

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restricted the use to within greenhouses only. This restriction was removed on December 21, 2007 "Amendment to Allow Outdoor Uses, Add Cooperators and Adjust Drench and Irrigation Rates". An Experimental Use Permit for use of S-ABA on grapes for color enhancement (# 73049-EUP-4) was issued on March 20, 2008. The Grape EUP petition also included establishment of a temporary exemption from the requirement of a tolerance for residues of the biochemical pesticide S-Abscisic Acid in or on grapes, 40 CFR Part 180 [EPA-HQ-2008-0092; FRL-8357-4] "S-Abscisic Acid, Temporary Exemption From The Requirements of a Tolerance".

This current registration petition is part of a joint review project between US EPA and Australian Pesticide and Veterinary Medicine Authority (APVMA), and is being concurrently submitted to both the EPA and APVMA.

This request for a pesticide registration is for the new biochemical active ingredient S-Abscisic Acid (VBC-30054), and two formulations of that active (VBC-30101 a liquid formulation and VBC-30051 a solid formulation), for use on ornamental and grape crops. The Product names for these formulations are; ConTego Pro® SG and ConTego Pro® SL (for VBC-30051 and VBC-30101 respectively) for use on ornamentals and ProTone® SG and ProTone® SL (for VBC-30051 and VBC-30101 respectively) for use on grapes.

Data on a third end product formulation (VBC-30074) has previously been submitted to EPA and will be submitted to APVMA, even though this formulation is not being included in the full registration request, because the included formulation VBC-30101 is an identical formulation (identical to VBC-30074) and the VBC-30101 data set relies on data generated with VBC-30074. Because these two formulations are essentially identical, we are requesting that the VBC-30074 data be transferable to VBC-30101. This is specifically mentioned to try and overt confusion regarding submitting formulation data and not submitting a request for the registration of that formulation, and to make clear the request for bridging the data from VBC-30074 to VBC-30101. VBC-30074 data supports the VBC-30101 registration request.

Studies previously submitted to EPA will be referenced by MRID # and not resubmitted to EPA, but all studies will be submitted to APVMA for their review and records. In addition to copies of the full studies, a 'Robust Study Summary' for each study (in the OECD format, along with summary reviews, Documents L and M) will be submitted to both agencies. These summaries were requested by APVMA, are not typically part of an EPA submission, but will be included in a separate binder within the EPA format as an effort in transparency and completeness. All studies will be submitted to both agencies, even if the data is not specifically required by one of the agencies. all studies supporting this registration request, including those previously submitted, are listed in the OECD study list. EPA specific submission forms will not be included in the APVMA submission, and visa versa. Separate product labels will be submitted to EPA and APVMA, and Efficacy data will be submitted to APVMA only.

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An Extension of the current EPA 'Temporary Exemption from the Requirements of a Tolerance' to a permanent exemption is being requested from both agencies, based on the natural and ubiquitous occurrence of S-ABA and it's lack of any toxicological response in the mammalian and ecological toxicity testing.

S-Abscisic Acid is a naturally occurring plant growth hormone. It is naturally synthesized, utilized and metabolized in the course of natural plant physiology. It has been found at various concentrations in all plants in which it was looked for, and it's concentration is known to naturally fluctuate quite significantly depending upon the stage and environmental conditions of the plant.

The S-Abscisic Acid 'Technical Grade Active Ingredient (TGAI)' being registered by Valent BioSciences is a natural product produced by a fermentation process. It is subsequently isolated and purified to give the Technical Grade Active Ingredient (TGAI) used in the Valent End Use products. This TGAI, being a fermentation product, is produced by an organism and therefore identical to S-ABA produced by other organism in the environment.

Valent BioSciences has performed the acute toxicity tests (acute oral, acute dermal, acute inhalation, primary eye irritation, primary skin irritation, and dermal sensitization), subchronmic toxicity tests (90-day oral repeat dose, 21-day dermal repeat dose, and 90-day inhalation repeat dose), Mutagenicity testing [Reverse Mutation; *Salmonella typhimurium* and *Escherichia coli* tester strain., *In vivo* clastogenic activity, micronuclei in polychromatic erythrocytes in CD-1 (ICR)BR mouse bone marrow, and chromosomal aberrations in cultured Chinese hamster ovary (CHO) cells], prenatal developmental toxicity, and a reporter gene assay for endocrine disruption evaluation, on the TGAI (S-Abscisic Acid). All of these studies were performed at standard limit doses and all of these studies showed no toxicity of the tested material. The only response seen in any test was a mild irritation effect in the primary eye irritation test which cleared in all animals by the end of the test.

A 21-day repeat-dermal exposure study was performed based on the pre-registration conference input received from the EPA (pre-registration conference held between Valent BioSciences and EPA on July 13, 2005). During this conference Valent BioSciences was advised to perform a 21-day repeat-exposure dermal toxicity study to support the full registration because of the potential for repeat exposure from the ornamental use pattern.

The formulated End Use Products, containing 10% or 20% active, also showed a lack of toxicity. The acute tests were performed on VBC-30051 (a 20% active solid formulation) and on VBC-30074 (a 10% active aqueous liquid formulation). The VBC-30101 product (a 10% active aqueous liquid formulation) is almost identical to the VBC-30074 formulation (with the addition of [redacted] each at less than 0.5%). The eye irritation test for VBC-30101 was performed and gave the same results as the eye irritation test for VBC-30074, demonstrating on the only test that showed any observable effect that these two formulated products are toxicologically the same.

Waivers are being requested for the additional acute toxicity testing of VBC-30101 with substitution of the test data obtained from VBC-30074 (an essentially identical formulation).

Because S-ABA is one of the major natural plant growth regulators, considerable information is present in the published literature. This literature information regarding the natural occurrence in various plants and other organisms and its concentrations, biosynthesis, metabolism and degradation, and the biochemical and physiological effects, is presented in a summary document which is accompanied by the literature articles referenced.

Acute ecological toxicity testing has been conducted by Valent BioSciences with Bobwhite quail, rainbow trout, Daphnia Magna, Honey bee (contact and oral), and earthworm all under GLP. No toxicity was observed at the limit doses for these species.

Additionally, results of similar testing performed by the TGAI manufacturer are given for a complete presentation of all information in our possession, but are not maintained to be GLP studies. The species tested by the manufacturer are; zebra fish, Italian worker bee (contact and oral), silk worm, and Japanese quail. The rates used were in many cases over 10 times higher than what was used in the GLP limit tests performed by Valent BioSciences. Similar results of low to no toxicity were seen.

Non-target plant testing (vegetative vigor and seedling emergence) was performed with the VBC-30074 formulation. No toxic effects and little overall effect were observed in these tests. Additional testing beyond the tier I level is not considered necessary and Valent BioSciences has requested a wavier from additional testing.

Because of the low acute toxicity to these species at the high limit doses used, testing with the formulations which contain only 10 to 20% active ingredient is not believed to be informative. All 'non-active' formulation ingredients are themselves not toxic and therefore the total formulation would be less toxic than what was observed for the TGAI concentrate. Because of the low acute toxicity seen at rates higher than the limit doses, and because S-ABA is already present in nature at low doses in all diets that contain plant materials, dietary studies and higher tier studies with fish, fowl or other ecological species are not believed to be informative. Valent is requesting a waiver from the requirements for this toxicity testing of the end use products.

This request for a pesticide registration is for the new biochemical active ingredient S-Abscisic Acid (VBC-30054) TGAI for manufacturing use only, and two formulations of that active (VBC-30101 a liquid concentrate formulation and VBC-30051 a soluble granule formulation), for use on ornamental and grape crops. The Product names for these formulations are; ConTego Pro® SG and ConTego Pro® SL for use on ornamentals (for VBC-30051 and VBC-30101 respectively) and ProTone® SG and ProTone® SL for use on grapes (for VBC-30051 and VBC-30101 respectively). Extension of the current 'Temporary Exemption from the Requirements of a Tolerance' to a 'Permanent Exemption from the Requirement of a Tolerance' is also being requested.

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Valent BioSciences believes this action fits the category of B590 "New Active ingredient; Food use; establish tolerance exemption", with a cost of $26,250.00 and a PRIA timeline of 16 months. Valent BioSciences has previously submitted payment for this registration action; [Pay.gov tracking ID: 24UFQO6M, Name of account: Valent BioSciences Corp., Payment amount: $26,250.00, Payment date: Dec 31, 2007].

This EPA application is organized as follows:

Administrative Documents
- Cover Letter
- Notice of Filing

VBC-30054 (TGAI)
- Form 8570-1 Application for Pesticide Registration
- Form 8570-34 Certification with Respect to Citation of Data
- Form 8570-35 Data Matrix
- Form 8570-4 CSF (VBC-30054, Technical Material)

VBC-30051 (Soluble Granular Formulation)
- Form 8570-1 Application for Pesticide Registration
- Form 8570-34 Certification with Respect to Citation of Data
- Form 8570-35 Data Matrix
- Form 8570-4 CSF (VBC-30051, Soluble Granule)

VBC-30101 (Soluble Liquid Formulation)
- Form 8570-1 Application for Pesticide Registration
- Form 8570-34 Certification with Respect to Citation of Data
- Form 8570-35 Data Matrix
- Form 8570-4 CSF (VBC-30101 Soluble Liquid)

Transmittal Document
List of Studies by Type and Author (OECD Formatted)

Section A - Chemical and Physical Properties
Section B - Proposed Use Label,
- TGAI Label, Manufacturing Use Only
- Master Label (VBC-30051 Soluble Granule formulation)
- Master Label (VBC-30101 Soluble Liquid formulation)

Section C - Toxicology Data
Section D - Residue Summary & Residue Analytical methods
Section E - Tolerance - Tolerance Exemption

Included within this EPA application, Valent BioSciences Corp. is attaching a transmittal document that lists 43 new studies in support of this registration request.

VALENT BIOSCIENCES CORPORATION

Please be aware that Valent BioSciences has submitted along with the Product Use labels included in Section B, five additional copies of each label.

Please contact me at (847)-968-4726 if I can be of any assistance during the review of this application.

Sincerely,

Thomas Bade Ph.D.
Regulatory Manager
Valent BioSciences

Transmittal Document
Application for Registration of
S-Abscisic Acid (S-ABA)

Submitter: Valent BioSciences Corp.
870 Technology Way
Libertyville, IL 60048

Regulatory Action: In support of the Biochemical pesticide registration of end-use Products of S-Abscisic Acid (Natural Plant Growth regulator) for use on ornamentals (to mitigate the effects of environmental stress) and on grapes (to enhance color development).

Transmittal Date: July 7, 2008

Listing of Submitted Studies:

Document 1

Title: Analysis and Certification of Product Ingredients in Five Batches of Technical S-Abscisic Acid
Data requirements: 40 CFR § 151-13
OPPTS 830.1700
Study Date: October 18, 2007
Performing Laboratory: PTRL West, Inc.
625-B Alfred Nobel Drive
Hercules, CA 94547
Project ID: 1473W

MRID No.: **47470401**

Document 2

Title: Product Identity Confidential Statement of Formula VBC-30101 (S-ABA, S-Abscisic Acid Liquid Formulation)
Data requirements: 40 CFR § 151-10, § 151-11, § 151-12,
OPPTS 880.1100, 880.1200, 880.1400
Study Date: January 3, 2008
Performing Laboratory: Valent BioSciences Corporation
870 Technology Way
Libertyville, IL 60048
Project ID: S-ABA 30101; 127-1

MRID No.: **47470402**

Document 3

Title: S-Abscisic Acid: VBC-30054, Technical Powder,
Product Chemistry: Certification of Limits
Data requirements: 40 CFR § 151-15
OPPTS 830.1750
Study Date: January 3, 2008
Performing Laboratory: Valent BioSciences Corporation
870 Technology Way
Libertyville, IL 60048
Project ID: S-ABA 30101; 127-2

MRID No.: 47470403

Document 4

Title: Analysis of S-Abscisic Acid in Five Lots of VBC-30051 Formulation, by High Performance Liquid Chromatography
Data requirements: 40 CFR § 151-13,
Study Date: December 14, 2007
Performing Laboratory: Valent BioSciences Corp. Research Center
6131 Oakwood Road
Long Grove, IL 60047
Project ID: VBCL07-48060-07

MRID No.: 47470404

Document 5

Title: Analysis of S-Abscisic Acid in Five Lots of VBC-30101 Formulation, by High Performance Liquid Chromatography

Data requirements: 40 CFR § 151-13,
Study Date: February 15, 2008
Performing Laboratory: Valent BioSciences Corp. Research Center
6131 Oakwood Road
Long Grove, IL 60047
Project ID: VBCL08-48060-01

MRID No.: 47470405

Document 6

Title: Stability of S-Abscisic Acid Active Ingredient to Normal and Elevated Temperatures, Metals, and Metal Ions and Oxidizing Reducing Properties of S-Abscisic Acid Active Ingredient.
Data requirements: OPPTS 830.6313, 830.6314,
Study Date: September 5, 2007
Performing Laboratory: PTRL West, Inc.
625-B Alfred Nobel Drive
Hercules, CA 94547
Project ID: 1618W
PTRL Report ID: 1618W-1

MRID No.: **47470406**

Document 7

Title: Accelerated Storage Stability of VBC-30051 at Elevated Temperatures

Data requirements: OPPTS 830.6313
Study Date: June 13, 2007
Performing Laboratory: PTRL West, Inc.
625-B Alfred Nobel Drive
Hercules, California 94547
Project ID: PTRL West # 1612W
Report ID: PTRL West # 1612W-001

MRID No.: **47470407**

Document 8

Title: Accelerated Storage Stability of VBC-30074 at Elevated Temperatures

Data requirements: OPPTS 830.6313
Study Date: June 13, 2007
Performing Laboratory: PTRL West, Inc.
625-B Alfred Nobel Drive
Hercules, California 94547
Project ID: PTRL West # 1613W
Report ID: PTRL West # 1613W-001

MRID No.: **47470408**

Document 9

Title: Accelerated Storage Stability of VBC-30101 at Elevated Temperatures

Data requirements: OPPTS 830.6313
Study Date: January 14, 2008
Performing Laboratory: PTRL West, Inc.
625-B Alfred Nobel Drive
Hercules, California 94547
Project ID: PTRL West # 1728W
Report ID: PTRL West # 1728W-001

MRID No.: 47470409

Document 10

Title: VBC-30054 Physico-Chemical Properties

Data requirements: 40 CFR § 151-10
Study Date: December 5, 2007
Performing Laboratory: Huntingdon Life Science Ltd.
Woolley Road
Alconbury, Huntingdon
Cambridgeshire PE28 4HS, England
Project ID: ZAB/0083/072858

MRID No.: 47470410

Document 11

Title: Solubility of S-Abscisic Acid in Organic Solvents

Data requirements: OPPTS 830.7840
Study Date: March 26, 2008
Performing Laboratory: PTRL West, Inc.
625-B Alfred Nobel Drive
Hercules, California 94547
Project ID: PTRL West # 1730W
Report ID: PTRL West # 1730W-1

MRID No.: 47470411

Document 12

Title: Hydrolysis of S-Abscisic Acid at pH 4, 7 and 9

Data requirements: OPPTS 835.2110
Study Date: April 24, 2008
Performing Laboratory: PTRL West, Inc.
625-B Alfred Nobel Drive
Hercules, California 94547
Project ID: PTRL West # 1729W
Report ID: PTRL West # 1729W-1

MRID No.: **47470412**

Document 13

Title: Evaluation of the Environmental Safety of S-Abscisic Acid

Data requirements: Not Specified
Study Date: November 30, 2004
Performing Laboratory: Performing Laboratory: Nanjing Institute of Environmental Sciences, State Environmental Protection Administration of Chinese, for Sichuan Lomon Fusheng Biotechnology Co. Ltd.,

Test Number: 2004B-04

MRID No.: **47470413**

Document 14

Title: Certification of S-ABA Reference Standards (Lot # 030806D1)

Data requirements: OPPTS 830.1550
Study Date: December 22, 2004
Performing Laboratory: Analytical Chemistry, deCODE chemistry
2501 Davey Road
Woodridge, IL 60517
Project ID: VAL0105DX
Report #: REP-RC-2004-048

MRID No.: **47470414**

Document 15

Title: Retest of S-ABA Reference Standards (Lot # 030806D1)

Data requirements: OPPTS 830.1550
Study Date: August 4, 2005
Performing Laboratory: Analytical Chemistry, deCODE chemistry
2501 Davey Road
Woodridge, IL 60517
Project ID: VAL0107DX
Report #: REP-RC-2005-039

MRID No.: 47470415

Document 16

Title: VBC 30101: Supplement to Physical and Chemical Properties: Justification for Waivers from Flammability, Explodability, and Corrosion Characteristics.

Data requirements: 40 CFR, OPPTS 830.6315, 830.6316, 830.6320
Study Date: February 8, 2008
Performing Laboratory: Valent BioSciences Corporation
870 Technology Way, Suite 100
Libertyville, IL 60048
Project ID: S-ABA 30101; 127-3

MRID No.: 47470416

Document 17

Title: Physical Properties of VBC-30051

Data requirements: 40 CFR § 151-10
Study Date: December 5, 2007
Performing Laboratory: PTRL West, Inc.
625-B Alfred Nobel Drive
Hercules, California 94547
Project ID: PTRL West # 1614W

MRID No.: 47470417

Document 18

Title: Physical Properties of VBC-30074

Data requirements: 40 CFR § 151-10
Study Date: October 17, 2007
Performing Laboratory: PTRL West, Inc.
625-B Alfred Nobel Drive
Hercules, California 94547
Project ID: PTRL West # 1615W

MRID No.: 47470418

Document 19

Title: Physical Properties of VBC-30101

Data requirements: OPPTS 830.6302, 830.6303, 830.6304, 830.7000, 830.7100, 830.7300
Study Date: January 14, 2008
Performing Laboratory: PTRL West, Inc.
625-B Alfred Nobel Drive
Hercules, California 94547
Project ID: PTRL West # 1720W
Report ID: PTRL West # 1720W-1

MRID No.: 47470419

Document 20

Title: VBC-30101 Primary Eye Irritation Study in Rabbits

Data requirements: 40 CFR § 152-13, OPPTS 870.2400
Study Date: December 12, 2007
Performing Laboratory: Product Safety Laboratories
2394 Highway 130
Dayton, New Jersey 08810
Project ID: 23416

MRID No.: 47470420

Document 21

Title: Justification for Waiver Request from the Biochemical Pesticide Toxicity Data Requirements For Acute Oral Toxicity Testing For VBC-30101

Data requirements: 40 CFR § 152-10, OPPTS 870.1100
Study Date: January 3, 2008
Performing Laboratory: Valent BioSciences Corporation
870 Technology Way, Suite 100
Libertyville, IL 60048
Project ID: S-ABA 30101; 127-11

MRID No.: **47470501**

Document 22

Title: Justification for Waiver Request from the Biochemical Pesticide Toxicity Data Requirements For Acute Dermal Toxicity Testing For VBC-30101

Data requirements: 40 CFR § 152-11, OPPTS 870.1200
Study Date: January 3, 2008
Performing Laboratory: Valent BioSciences Corporation
870 Technology Way, Suite 100
Libertyville, IL 60048
Project ID: S-ABA 30101; 127-12

MRID No.: **47470502**

Document 23

Title: Justification for Waiver Request from the Biochemical Pesticide Toxicity Data Requirements For Inhalation Toxicity Testing For VBC-30101

Data requirements: 40 CFR § 152-12, OPPTS 870.1300
Study Date: January 3, 2008
Performing Laboratory: Valent BioSciences Corporation
870 Technology Way, Suite 100
Libertyville, IL 60048
Project ID: S-ABA 30101; 127-13

MRID No.: **47470503**

Document 24

Title: Justification for Waiver Request from the Biochemical Pesticide Toxicity Data Requirements For Dermal Irritation Toxicity Testing For VBC-30101

Data requirements: 40 CFR § 152-14, OPPTS 870.2500
Study Date: January 3, 2008
Performing Laboratory: Valent BioSciences Corporation
870 Technology Way, Suite 100
Libertyville, IL 60048
Project ID: S-ABA 30101; 127-14

MRID No.: **47470504**

Document 25

Title: Justification for Waiver Request from the Biochemical Pesticide Toxicity Data Requirements For Dermal Sensitization Toxicity Testing For VBC-30101

Data requirements: 40 CFR § 152-15, OPPTS 870.2600
Study Date: January 3, 2008
Performing Laboratory: Valent BioSciences Corporation
870 Technology Way, Suite 100
Libertyville, IL 60048
Project ID: S-ABA 30101; 127-15

MRID No.: **47470505**

Document 26

Title: Justification for Waiver Request from the Biochemical Pesticide Toxicity Data Requirements For 90-Day Repeat Inhalation Toxicity Testing For VBC-30101

Data requirements: 40 CFR § 152-22, OPPTS 870.3465
Study Date: January 3, 2008
Performing Laboratory: Valent BioSciences Corporation
870 Technology Way, Suite 100
Libertyville, IL 60048
Project ID: S-ABA 30101; 127-16

MRID No.: **47470506**

Document 27

Title: VBC-30054: One-Week Toxicity Dose Range Finding Study in Rats with Dermal Administration

Data requirements: OPPTS 830.7000
Study Date: January 23, 2008
Performing Laboratory: Charles River Laboratories
Tranent
Edinburgh EH33 2NE, UK
Project ID: 458194
Report No: 27954 Report Amendment 1

MRID No.: **47470507**

Document 28

Title: VBC-30054: 3 Week Toxicity Study in Rats with Dermal Administration

Data requirements: OPPTS 830.7000
Study Date: February 1, 2008
Performing Laboratory: Charles River Laboratories
Tranent
Edinburgh EH33 2NE, UK
Project ID: 458215
Report No: 27971

MRID No.: **47470508**

Document 29

Title: VBC-30054: 4 Week Toxicity Study in Rats with Administration by the Diet

Data requirements: 40 CFR, OPPTS 870.3100
Study Date: February 1, 2008
Performing Laboratory: Charles River Laboratories
Tranent
Edinburgh EH33 2NE, UK
Project ID: 457866
Report No: 27720

MRID No.: **47470509**

Document 30

Title: VBC-30054: 13 Week Toxicity Study in Rats with Administration by the Diet

Data requirements: 40 CFR § 152.20, OPPTS 870.3100
Study Date: February 1, 2008
Performing Laboratory: Charles River Laboratories
Tranent
Edinburgh EH33 2NE, UK
Project ID: 457871
Report No: 28084

MRID No.: **47470510**

Document 31

Title: VBC-30054: Preliminary Developmental Toxicity Study in Rats

Data requirements: 40 CFR § 152-23, OPPTS 870.3700
Study Date: March 21, 2008
Performing Laboratory: Charles River Laboratories
Tranent
Edinburgh EH33 2NE, UK
Project ID: 494845
Report N0.: 28566

MRID No.: **47470511**

Document 32

Title: A Prenatal Developmental Toxicity Study of S-Abscisic Acid in Rats

Data requirements: OPPTS 870.3700, OECD 414
Study Date: May 5, 2008
Performing Laboratory: WIL Research Laboratories, LLC
1407 George Road
Ashland, OH 44805
Project ID: WIL-505004

MRID No.: **47470512**

Document 33

Title: Reporter gene assay for abscisic acid (ABA) using human estrogen and androgen receptors

Data requirements: 40 CFR § 152-24, OPPTS 870.3700
Study Date: December 14, 2007
Performing Laboratory: Environmental Health Science Laboratory
Sumitomo Chemical Co., Ltd.
1-98, 3-chome
Kasugade-Naka
Konohana-Ku
Osaka, Japan
Project No.: VBC-SCC ABA 12-14-07

MRID No.: **47470513**

Document 34

Title: Abscisic Acid: An Acute Toxicity Study With the Earthworm In An Artificial Soil Substrate

Data requirements: OECD Guideline 207
Study Date: March 12, 2008
Performing Laboratory: Wildlife International, Ltd.
8598 Commerce Drive
Easton, Maryland 21601, USA
Project ID: 529-119

MRID No.: **47470514**

Document 35

Title: Environmental Safety Assessment of Natural Abscisic Acid

Data requirements: Not Specified
Study Date: June 25, 2000
Performing Laboratory: Performing Laboratory: Nanjing Institute of Environmental Sciences, State Environmental Protection Administration of Chinese, for Sichuan Lomon Fusheng Biotechnology Co. Ltd.,
Test Number: June 2000

MRID No.: **47470515**

Document 36

Title: VBC-30074: A Toxicity Test to Determine the Effects of The Test Substance on Vegetative Vigor of Ten Species of Plants

Data requirements: OPPTS 850.4150
Study Date: April 2, 2008
Performing Laboratory: Wildlife International, Ltd.
8598 Commerce Drive
Easton, Maryland 21601, USA
Project ID: 529-115

MRID No.: **47470516**

Document 37

Title: VBC-30074: A Toxicity Test to Determine the Effects of The Test Substance on Seedling Emergence of Ten Species of Plants

Data requirements: OPPTS 850.4100
Study Date: April 2, 2008
Performing Laboratory: Wildlife International, Ltd.
8598 Commerce Drive
Easton, Maryland 21601, USA
Project ID: 529-116

MRID No.: **47470517**

Document 38

Title: Background of Abscisic Acid (ABA) A Plant Growth Regulator for use on Grapes and Ornamentals

Data requirements: Background Information, Summary of Published Literature
Study Date: May 23, 2008
Performing Laboratory: Valent BioSciences Corp. Research Center
6131 Oakwood Road
Long Grove, IL 60047
Project ID: ABA – LS2

MRID No.: **47470518**

Document 39

Title: Copies of Referenced Papers in 'Background of Abscisic Acid (ABA) A Plant Growth Regulator for use on Grapes and Ornamentals'

Data requirements: Background Information, Summary of Published Literature
Study Date: May 29, 2008
Performing Laboratory: Valent BioSciences Corp. Research Center
6131 Oakwood Road
Long Grove, IL 60047
Project ID: ABA – LS2 REF

MRID No.: **47470519**

Document 40

Title: Characterization of the 1'-4'-*trans*-diol of Abscisic Acid Reference Standard (VBC-30084)

Data requirements: 40 CFR 160.105(a) Test, Control and References Substances Characterization
Study Date: March 30, 2007
Performing Laboratory: Valent BioSciences Corp. Research Center
6131 Oakwood Road
Long Grove, IL 60047
Project ID: VBCL07-48060-01

MRID No.: **47470520**

Document 41

Title: Abscisic Acid (S-ABA) Request for a waiver from the Biochemical Pesticide Registration Requirements for Avian Dietary Toxicity Testing

Data requirements: OPPTS 850.2200
Study Date: May 30, 2008
Performing Laboratory: Valent BioSciences Corp.
870 Technology Way
Libertyville, IL 60048
Project ID: S-ABA 30054; 058-1

MRID No.: **47470521**

Document 42

Title: Abscisic Acid (S-ABA) Request for a waiver from the Biochemical Pesticide Registration Requirements for Multi Residue Testing Method

Data requirements: OPPTS 860.1360

Study Date: May 30, 2008
Performing Laboratory: Valent BioSciences Corp.
870 Technology Way
Libertyville, IL 60048
Project ID: S-ABA 30054; 058-2

MRID No.: **47470522**

Document 43

Title: S-Abscisic Acid (S-ABA), ProTone® SG, "Australian efficacy data S-ABA use on Grapes"

Data requirements: NA

Study Date: July, 2008
Performing Laboratory: Valent BioSciences
A Division of Sumitomo Chemical Australia Pty Ltd.

Project ID: Australian Efficacy – Grape Use

MRID No.: **47470523**

Company Official: Thomas Bade 7/7/08
Signature

Company Name: Valent BioSciences Corporation

Company Contact: Thomas Bade Ph.D. 847-968-4726
Regulatory Manager Phone

DATA PACKAGE BEAN SHEET

Date: 06-Aug-2008

Decision #: 397560
DP #: (355254)
PRIA
Parent DP #:
Submission #: 832265

* * * Registration Information * * *

Registration: 73049-UAN - S-ABSCISIC ACID, (S-ABA) TECHNICAL GRADE ACTIVE IN

Company: 73049 - VALENT BIOSCIENCES CORPORATION

Risk Manager: RM 91 - Driss Benmhend - (703) 308-9525 Room# PY1 S-8948

Risk Manager Reviewer: Jay Pfeifer JPFEIFER

Sent Date: _____ Calculated Due Date: 21-Nov-2009 Edited Due Date: _____

Type of Registration: Product Registration - Section 3

Action Desc: (B590) NEW AI;FOOD USE;MICROBIAL/BIOCHEMICAL WITH EXEMPTION;

Ingredients: 272000, Abscisic acid(99.3%)

* * * Data Package Information * * *

Expedite: ○ Yes ● No Date Sent: 06-Aug-2008 Due Back: _____

DP Ingredient: 272000, Abscisic acid

DP Title: Eco & Efficacy

CSF Included: ● Yes ○ No Label Included: ● Yes ○ No Parent DP #:

Assigned To		Date In	Date Out		
Organization:	BPPD / BPB	06-Aug-2008		Last Possible Science Due Date:	29-Jul-2008
Team Name:	RM 91	06-Aug-2008		Science Due Date:	
Reviewer Name:	Jones, Russell	06-Aug-2008		Sub Data Package Due Date:	
Contractor Name:					

* * * Studies Sent for Review * * *

Printed on Page 2

* * * Additional Data Package for this Decision * * *

Printed on Page 3

* * * Data Package Instructions * * *

Hold until Peer Review. No Due date yet.

DP#: (355254) *** Studies Sent for Review *** Decision#: (397560)

MRID	MRID Status	Citation Reference	Guideline
47470514		Porch, J.; Krueger, H. (2008) Abscisic Acid: An Acute Toxicity Study with the Earthworm in an Artificial Soil Substrate: Final Report. Project Number: 529/119. Unpublished study prepared by Wildlife International, Ltd. 33 p.	
47470515		Zhu, Z.; Shan, Z.; Cai, D. (2000) Environmental Safety Assessment of Natural Abscisic Acid. Project Number: JUNE/2000. Unpublished study prepared by Nanjing Institute of Environmental Sciences. 19 p.	
47470516		Porch, J.; Krueger, H.; Martin, K. (2008) VBC-30074: A Toxicity Test to Determine the Effects of the Test Substance on Vegetative Vigor of Ten Species of Plants: Final Report. Project Number: 529/115. Unpublished study prepared by Wildlife International, Ltd. 86 p.	850.4150/Terrestrial plant toxicity, Tier 1 (vegetative vigor)
47470517		Porch, J.; Martin, K.; Krueger, H. (2008) VBC-30074: A Toxicity Test to Determine the Effects of the Test Substance on Seedling Emergence of Ten Species of Plants: Final Report. Project Number: 529/116. Unpublished study prepared by Wildlife International, Ltd. 68 p.	850.4100/Terrestrial plant toxicity, Tier 1 (seeding emergence)
47470520		Baldi, B. (2007) Characterization of the 1',4'-trans-diol of Abscisic Acid Reference Substance (VBC-30084): Final Report. Project Number: VBCL07/48060/01. Unpublished study prepared by Valent Biosciences Corp. 25 p.	
47470521		Bade, T. (2008) Abscisic Acid (S-ABA) Request for a Waiver from the Biochemical Pesticide Registration Requirements for Avian Dietary Toxicity Testing. Project Number: S/ABA/30054/058/1. Unpublished study prepared by Valent Biosciences Corporation. 9 p.	850.2200/Avian dietary toxicity test

DATA PACKAGE BEAN SHEET

Date: 06-Aug-2008

Decision #: 397560
DP #: (355253)
PRIA
Parent DP #:
Submission #: 832265

* * * Registration Information * * *

Registration: 73049-UAN - S-ABSCISIC ACID, (S-ABA) TECHNICAL GRADE ACTIVE IN

Company: 73049 - VALENT BIOSCIENCES CORPORATION

Risk Manager: RM 91 - Driss Benmhend - (703) 308-9525 Room# PY1 S-8948

Risk Manager Reviewer: Jay Pfeifer JPFEIFER

Sent Date: _____ Calculated Due Date: 21-Nov-2009 Edited Due Date: _____

Type of Registration: Product Registration - Section 3

Action Desc: (B590) NEW AI;FOOD USE;MICROBIAL/BIOCHEMICAL WITH EXEMPTION;

Ingredients: 272000, Abscisic acid(99.3%)

* * * Data Package Information * * *

Expedite: ● Yes ○ No Date Sent: 06-Aug-2008 Due Back: _____

DP Ingredient: 272000, Abscisic acid

DP Title: Residue

CSF Included: ● Yes ○ No Label Included: ● Yes ○ No Parent DP #: _____

	Assigned To	Date In	Date Out	
Organization:	BPPD / BPB	06-Aug-2008		Last Possible Science Due Date: 29-Jul-2008
Team Name:	RM 91	06-Aug-2008		Science Due Date:
Reviewer Name:	Jones, Russell	06-Aug-2008		Sub Data Package Due Date:
Contractor Name:				

* * * Studies Sent for Review * * *

Printed on Page 2

* * * Additional Data Package for this Decision * * *

Printed on Page 3

* * * Data Package Instructions * * *

Combine with other Tox Waiver Requests for ABA

DP#: (355253) *** Studies Sent for Review *** Decision#: (397560)

MRID	MRID Status	Citation Reference	Guideline
47470522		Bade, T. (2008) Abscisic Acid (S-ABA) Request for a Waiver from the Biochemical Pesticide Registration Requirements for Multi Residue Testing Method. Project Number: S/ABA/30054/058/2. Unpublished study prepared by Valent Biosciences Corporation. 8 p.	860.1360/Multiresidue method

DATA PACKAGE BEAN SHEET

Date: 06-Aug-2008

Decision #: 397560
DP #: (355252)
PRIA
Parent DP #:
Submission #: 832265

* * * Registration Information * * *

Registration: 73049-UAN - S-ABSCISIC ACID, (S-ABA) TECHNICAL GRADE ACTIVE IN

Company: 73049 - VALENT BIOSCIENCES CORPORATION

Risk Manager: RM 91 - Driss Benmhend - (703) 308-9525 Room# PY1 S-8948

Risk Manager Reviewer: Jay Pfeifer JPFEIFER

Sent Date: _____ Calculated Due Date: 21-Nov-2009 Edited Due Date: _____

Type of Registration: Product Registration - Section 3

Action Desc: (B590) NEW AI;FOOD USE;MICROBIAL/BIOCHEMICAL WITH EXEMPTION;

Ingredients: 272000, Abscisic acid(99.3%)

* * * Data Package Information * * *

Expedite: ● Yes ○ No Date Sent: 06-Aug-2008 Due Back: _____

DP Ingredient: 272000, Abscisic acid

DP Title: ABA Tox

CSF Included: ● Yes ○ No Label Included: ● Yes ○ No Parent DP #: _____

Assigned To	Date In	Date Out	
Organization: BPPD / BPB	06-Aug-2008		Last Possible Science Due Date: 29-Jul-2008
Team Name: RM 91	06-Aug-2008		Science Due Date:
Reviewer Name: Alam, Wagi	07-Aug-2008		Sub Data Package Due Date:
Contractor Name:			

* * * Studies Sent for Review * * *

Printed on Page 2

* * * Additional Data Package for this Decision * * *

Printed on Page 3

* * * Data Package Instructions * * *

Please combine with other Valent ABA Review.

Review tox for acceptability of new ai/food use.

BPPD Preliminary Administrative/Scientific Screening Checklist

Date:7/22/08
EPA Reg. No. :73049-UAN (TGAI), ~~UAR, UAE~~
PRIA Code:B-590.0, 590.1, 590.2, 590.3
Active ingredient name: S-Abscisic acid (99%)
Biochemical/Microbial: TGAI/MP/EP: Biochemical TGAI
PASS

Admin Materials	Signed		Date	Absent	Comments
	Yes	No			
Form **8570-1** • All sections (where applicable completed to include Reg. No of substantial product if applicable • Is a cover letter included, if so, is there a request for DER's upon completion?	X		6/9/08		Application for registration of a TGAI, using a plant growth regulator. - Cover letter doesn't have a request for DER - -CSF is completely filled out with original signature - -No inerts listed five impurities are listed beside the Active ingredient - Ccconventional active present in the formulation - Supplier's source is provided - CAS# provided - No barnd name listed in the CSF -PCC of abscisic acid: 272000
CSF - Completely filled out & original signature (**EPA form 8570-4**) · inerts cleared? · conventional or antimicrobial actives present in formulation? · accurate information provided for suppliers/source? · CSF accurately reflects label? · Additional brand name listed in CSF · CAS# provided? · Are there any inerts that are 25(b) active and suspect of a different purpose in formulation other than what is stated? · Is there a range provided on the csf for the active ingredient (common for microbials) · Does the csf contain any inerts that are subject to revocation? · Is a pc code available? · If a pcc needs to be	X		6/9/08		

Admin Materials	Signed	Date	Absent	Comments
established, has the request been made? • If inert ingredient is water, is a source provided? • If product is a 100% repack, is this indicated? • **note all comments**				
Label • legible product label? • label accurately reflects csf? • Are the uses (Residential, Commercial,Ag) clearly stated w/o ambiguity? • **note all comments**				-legible product label with uses listed -label reflects CSF
Physical address of manufacturer on label to include EPA Establishment #				Physical address is provided, but not the EPA establishment number
Data Matrix - Two/one for jacket; one for FOIA **(EPA Form 8570-35)** • supports method of support? • reflects information reported in transmittal document and company cover letter? • Are all tier I biochemical/microbial data requirements for product chemistry, human health toxicology, non target organism fate and effects addressed either with MRID"s, own or N/A statement where applicable? • Have data waivers been requested? If so, are the data requirements (studies) listed on the data matrix? • Have data waiver volumes been provided (with separate MRID's and not part of the	X	6/9/08		Two copies for Dta Matrix provided - All tier I data (product chemistry) are submitted with this submission - Waiver requests are submitted in separate volume with separate MRID#s

Admin Materials	Signed		Date	Absent	Comments
administrative volume) which address the data requirements on a guideline by guideline basis? • Is Efficacy data present? Is HSRB review needed for the protocol? The submission must be flagged as ethics and/or HSRB review will be required. • **note all comments**					
Formulator's exemption form **(EPA form 8570-27)** • Is it completed? Is a registered source listed?				X	Not present, not required
Transmittal letters • accurately reflects what is reported on data matrix? • Does the data described align with the description per the application and cover letter? • **note all comments**	X		7/13/08		Transmittal letter reflects data matrix
Petition/amended petition if food tolerance or exemption/amended food tolerance or exemption • petition# assigned? • petition jacket included? • petition complete with sections A-G? • **note all comments - if there is not evidence of a petition # assigned and sect. A-G not present, package fails.**	X				Petition for exemption for tolerance requirement is submitted -petition no:8F7391 -Sections A-G present - petition jacket included
FR template if food tolerance or exemption/amended food tolerance or exemption • notice of filing template emailed to appropriate Chief/RAL? • component in the formulation not cleared food use • **note all comments - a NOF must be present to establish**					Notice of filing template present

Admin Materials	Signed		Date	Absent	Comments
a new tolerance exemption. Amendments to an existing tol. petition may be Agency initiated in which case a NOF would not expected to be present. (If unsure, check with branch team leader)					
Certification with Respect to Citation of Data Form **(EPA Form 8570-34)** - if required. State method of support and indicate the EPA reg. # of the cited product if applicable. • If repack, this form is not needed.	X		6/9/08		Selective method
Minutes on data requirements (pre-registration meeting)					
Active ingredient # (i.e. Chemical PC code) · more than one active? · are all actives housed in BPPD? · Is the active new? · If not new, when was the active registered? · Is this exclusive use? · Any data compensation issues suspected?					Single Active ingredient housed in BPPD PCC of Abscisic acid:
Jacket from EPA Identifying Symbol					73049-UAN
Are MRIDS assigned? (State Yes/No in comments)					Yes
Background Experimental Use Permit information, if applicable · request for temporary tol. exempt, tol. exemption or numeric tolerance? · **note all comments - refer to petition and fr section for critera.**					

Rev. 10/07

CHECKLIST FOR DATA PACKAGE SCIENCE SCREEN

Active Ingredients with PC codes: Abscisic acid: 272000
Product Name: Abscisic acid Technical
EPA Reg. No/File Symbol: 73049-UAN
Pettion # 8F7391 **PASS**

(Circle or Check Appropriate Boxes)

Product Type				
Biochemical, Microbial, or PIP		B	M	P
Food Use		Y		
Straight-chain Lepidopteran Pheromone (Biochemical Only)		N		
New Active Ingredient		Y		
Sec. 3 Registration		Y		
Experimental Use Permit		N		
IR-4 Submission		N		
Reduced Risk Product		Y		

Product Specific Information				
Data Requirement	TGAI	MP	EP	
Product Label	X			Complete
Product Chemistry				
CSF	X			Study submitted in MRID# 474704-01
Product Identity & Composition	X			Study submitted in MRID# 474704-02
Manufacturing Process	X			Study submitted in MRID# 474704-02
Description of the Formation of Impurities	X			Study submitted in MRID# 474704-02
Preliminary Analysis	X			Study submitted in MRID# 474704-04
Certified Limits	X			Study submitted in MRID# 474704-03
Enforcement Analytical Methods. five Batch analysis of Technical (determination of impurities)	X			Study submitted in MRID# 474704-01
Physical/Chemical Properties (as shown in 40 CFR 158.190 Table)	X			Study submitted in MRID# 474704-10, -11, -12
Tier I Toxicity (If no study, indicate in Comments if waiver submitted)				
Acute Oral/4-wk-toxicity-diet-rat	X			Study submitted in MRID# 474705-09
Acute Dermal/ 1 wk range –finding/3 wk-toxicity/rat	X			Study submitted in MRID# 474705-07, -08
Acute Inhalation	X			
I.C., I.P., I.V. Injection (Microbial only)				
Primary Dermal Irritation	X			
Primary Eye Irritation	X			Study submitted in MRID# 474704-20
Hypersensitivity				

(Conditionally required)				
Hypersensitivity Incidents (Conditionally required)				
Genotoxicity Studies (Biochemical only)				
Immune Response				
Tissue Culture (Microbial only)				
90-day Feeding (Biochemical only)	X			Study submitted in MRID# 474705-10
Structural Chromosomal aberration				
90-day Inhalation (Biochemical only)				
Teratogenicity/developmental toxicity (Biochemical only)				
Avian Acute Oral	X			Study cited in MRID# 470679-01
Avian Acute Dietary				
Freshwater Fish LC50	X			Study cited in MRID# 471314-02
Freshwater Invertebrate LC50	X			Study cited in MRID# 471314-01
Non-target Plants	X			Study cited in MRID# 471314-01
Non-Target Insects	X			Study cited in MRID# 471314-01
Honeybee Testing (Microbials only)				

Science Screen Comment Form

Active Ingredients with PC codes: Abscisic acid:272000
Product Name: Abscisic acid-Technical
Reg. No/File Symbol: 73049-UAN
RAL:
PASS
THIS FORM DOES NOT CONTAIN CONFIDENTIAL BUSINESS INFORMATION

Product Chemistry:
Data requirement is addressed by submitted studies seems to be adequate.

Toxicity:
Data requirement is addressed by submitted and cited studies seems to be adequate. For details please see the above form.

Non-target Organisms/ Environmental Fate and Expression:
Data requirement is addressed by cited studies in the data matrix seems to be adequate.

Product Performance (Efficacy):
Not present, not required

Residue:
Non-food use
Comments/Recommendations:

BPPD SCREEN PACKAGE

BPPD FRONT END: BPB/MPB: Team Leader _____**Drisss Benmhend**_

PRIA Code/Action Code: _____**B 590.0, 590.1, 590.2, and 590.3** Team/RAL: _

Product Name: _ **VBC-30051, VBC-30101** ,VBC-30054 **EPA ID No. 8F7391, 73049-UAN, UAR, UAE** 73049-UAN	**PRIA START DATE:** **DAY 21:**
Active Ingredient(s) **S-Abscisic Acid** 99% (TGAI)	

__X Food __X_ New Submission

___ Non Food___ Resubmission

Date In BPPD: _____**07/17/08**_____

Date To Screen: ___**07/17/08**_____

Date Expected From Screen: (5 Days from date in): __**07/24/08**_____
WA# 07-068

Nasrin Begum Nasrin Begum Act. Hours 4 Return to BPPD: 7/24/08

Received From Contractor (Date) 7/24/08

SCREEN PACKAGE NOTES:

Pre-Reg Meeting Minutes Attached? ____ Yes _X___ No

Submission complies with all applicable areas of checklists?
Indicate in detail on checklist forms when returned.

Additional Comments per Team Leader or Screener:

SCREEN STATUS

Administrative: ____(Pass)____ Fail

Scientific: ____(Pass)____ Fail

Ver. 072707 CG Times

Memorandum

Date: 7 / 16 / 08

To: BPPIS (91), Regulatory Manager

From: Information Services Branch, ITRMD

Your receipt of this data submission is not an indication that MRIDs for the enclosed studies have been posted to OPPIN.

We expect that it will be approximately 5 days from the above date before the study-level data is available in OPPIN.

If you have any questions about this process, please contact Teresa Downs (305-5363).

This is a:
- ☒ fully accepted submission
- ☐ partially accepted submission
- ☐ rejected submission

"Bade, Thomas" <Thomas.Bade@valent.com>

07/18/2008 10:12 AM

To John Jamula/DC/USEPA/US@EPA
cc "Herrero, Maria" <Maria.Herrero@valent.com>
bcc
Subject FW: Pay.Gov Payment Confirmation

Attached is the Pay.gov response email for the payment we discussed.

-----Original Message-----
From: Kelly, Kurt
Sent: Thursday, June 05, 2008 1:30 PM
To: Bade, Thomas
Subject: FW: Pay.Gov Payment Confirmation

Tom,

Below is the $26,250 payment details to EPA on December 31, 2007.

Kurt

-----Original Message-----
From: paygovadmin@mail.doc.twai.gov
[mailto:paygovadmin@mail.doc.twai.gov]
Sent: Friday, December 28, 2007 1:53 PM
To: Kelly, Kurt
Subject: Pay.Gov Payment Confirmation

THIS IS AN AUTOMATED MESSAGE. PLEASE DO NOT REPLY.

Your transaction has been successfully completed.

Payment Summary

Application Name: PRIA Service Fees
Pay.gov Tracking ID: 24UFQO6M
Payment Agency Tracking ID: 74037682391

Name On Account: Valent BioSciences Corp.
Payment Amount: $26,250.00
Payment Date: Dec 31, 2007 2:53:26 PM
Account Type: Business Checking
Routing Number: [redacted]
Bank Account Number: XXXX6214
Transaction Date: Dec 28, 2007 2:53:26 PM

Decision Number:
Registration Number: 73049-xx

Commercial/financial information may be entitled to confidential treatment

Transaction Detail Results

01/02/2008
10:35 AM ET

Agency: EPAOPPTS Application: PRIA Service Fees

Transaction Information

Pay.gov Tracking ID:	24UFQO6M
Agency Tracking ID:	74037682391
Account Holder Name:	Valent BioSciences Corp.
Transaction Date (ET):	12/28/2007 02:53 PM
Effective Date:	12/31/2007
Transaction Amount:	$26,250.00
Payment:	1 of 1
Collection Status:	Settled
ACH Type:	Debit
Deposit Ticket:	000276
Debit Voucher:	
Return Description:	

Custom Collection Fields

Registration Number	73049-xx

Please read instructions on reverse before completing form. Form Approved, OMB No. 2070-0060 Print Form

EPA United States Environmental Protection Agency Washington, DC 20460

[X] Registration [ ] Amendment [ ] Other

OPP Identifier Number

165

Application for Pesticide - Section I

1. Company/Product Number: Valent BioSciences / 73049-~~XX~~ UAN
2. EPA Product Manager:
3. Proposed Classification: [X] None [ ] Restricted
4. Company/Product (Name): Valent BioSciences / VBC-30054 (S-Abscisic Acid) TGAI MFG
PM#:
5. Name and Address of Applicant *(Include ZIP Code)*:
Valent BioSciences Corp.
870 Technology Way
Libertyville IL, 60048
[ ] *Check if this is a new address*
6. **Expedited Review.** In accordance with FIFRA Section 3(c)(3)(b)(i), my product is similar or identical in composition and labeling to:
EPA Reg. No. _____
Product Name _____

Section - II

[ ] Amendment - Explain below.
[ ] Resubmission in response to Agency letter dated _____
[ ] Notification - Explain below.
[ ] Final printed labels in response to Agency letter dated _____
[ ] "Me Too" Application.
[ ] Other - Explain below.

Explanation: Use additional page(s) if necessary. (For section I and Section II.)

Section - III

1. Material This Product Will Be Packaged In:

Child-Resistant Packaging	Unit Packaging	Water Soluble Packaging	2. Type of Container
[ ] Yes* [X] No	[ ] Yes [X] No	[ ] Yes [X] No	[ ] Metal [X] Plastic [ ] Glass [ ] Paper [ ] Other (Specify) _____
* *Certification must be submitted*	If "Yes" Unit Packaging wgt. / No. per container	If "Yes" Package wgt / No. per container	

3. Location of Net Contents Information: [X] Label [ ] Container
4. Size(s) Retail Container:
5. Location of Label Directions: [ ] On Label [X] On Labeling accompanying product
6. Manner in Which Label is Affixed to Product: [X] Lithograph [ ] Paper glued [ ] Stenciled [ ] Other _____

Section - IV

1. Contact Point *(Complete items directly below for identification of individual to be contacted, if necessary, to process this application.)*

Name	Title	Telephone No. (Include Area Code)
Thomas Bade P.hD.	Regulatory Manager	847-968-4726

Certification

I certify that the statements I have made on this form and all attachments thereto are true, accurate and complete. I acknowledge that any knowingly false or misleading statement may be punishable by fine or imprisonment or both under applicable law.

6. Date Application Received (Stamped)

2. Signature: Thomas Bade
3. Title: Regulatory Manager
4. Typed Name: Thomas Bade
5. Date: 6/9/08

EPA Form 8570-1 (Rev. 6-94) Previous editions are obsolete. White - EPA File Copy (original) Yellow - Applicant Copy

VALENT BIOSCIENCES
CORPORATION

870 TECHNOLOGY WAY
LIBERTYVILLE, IL 60048 - 800-323-9597

July 7, 2008

Ms Janet Anderson
Document Processing Desk
Office of Pesticide Programs (7504C)
U.S. Environmental Protection Agency
Room 266A, Crystal Mall 2
1921 Jefferson Davis Highway
Arlington, VA 22202

Attention: Mr. Chris Pfiefer
Regulatory Action Leader
Biochemical Pesticides Branch
Biopesticides and Pollution Prevention Division (7511P)
U.S. Environmental Protection Agency

Subject: Valent BioSciences Corp.
EPA Reg. No. 73049-XX,
Request for the Registration of S-Abscisic Acid (VBC-30054, TGAI), and
Two End Use Formulations (VBC-30051 & VBC-30101),
for use on Ornamental and Grape crops.

Dear Ms. Anderson,

The following pesticide registration application for the biochemical plant growth regulator S-Abscisic Acid (S-ABA) is submitted by Valent BioSciences Corp. for your consideration.

This is in continuation of many interactions and submissions presented to the United State Environmental Protection Agency (EPA). A pre-registration conference was held between Valent BioSciences and EPA on July 13, 2005. An Experimental Use Permit for use of S-ABA on Ornamentals for stress reduction (# 73049-EUP-3) was issued on February 15, 2007. This Experimental Use Permit (#72049-EUP-3) originally restricted the use to within greenhouses only. This restriction was removed on December

restricted the use to within greenhouses only. This restriction was removed on December 21, 2007 "Amendment to Allow Outdoor Uses, Add Cooperators and Adjust Drench and Irrigation Rates". An Experimental Use Permit for use of S-ABA on grapes for color enhancement (# 73049-EUP-4) was issued on March 20, 2008. The Grape EUP petition also included establishment of a temporary exemption from the requirement of a tolerance for residues of the biochemical pesticide S-Abscisic Acid in or on grapes, 40 CFR Part 180 [EPA-HQ-2008-0092; FRL-8357-4] "S-Abscisic Acid, Temporary Exemption From The Requirements of a Tolerance".

This current registration petition is part of a joint review project between US EPA and Australian Pesticide and Veterinary Medicine Authority (APVMA), and is being concurrently submitted to both the EPA and APVMA.

This request for a pesticide registration is for the new biochemical active ingredient S-Abscisic Acid (VBC-30054), and two formulations of that active (VBC-30101 a liquid formulation and VBC-30051 a solid formulation), for use on ornamental and grape crops. The Product names for these formulations are; ConTego Pro® SG and ConTego Pro® SL (for VBC-30051 and VBC-30101 respectively) for use on ornamentals and ProTone® SG and ProTone® SL (for VBC-30051 and VBC-30101 respectively) for use on grapes.

Data on a third end product formulation (VBC-30074) has previously been submitted to EPA and will be submitted to APVMA, even though this formulation is not being included in the full registration request, because the included formulation VBC-30101 is an identical formulation (identical to VBC-30074) and the VBC-30101 data set relies on data generated with VBC-30074. Because these two formulations are essentially identical, we are requesting that the VBC-30074 data be transferable to VBC-30101. This is specifically mentioned to try and overt confusion regarding submitting formulation data and not submitting a request for the registration of that formulation, and to make clear the request for bridging the data from VBC-30074 to VBC-30101. VBC-30074 data supports the VBC-30101 registration request.

Studies previously submitted to EPA will be referenced by MRID # and not resubmitted to EPA, but all studies will be submitted to APVMA for their review and records. In addition to copies of the full studies, a 'Robust Study Summary' for each study (in the OECD format, along with summary reviews, Documents L and M) will be submitted to both agencies. These summaries were requested by APVMA, are not typically part of an EPA submission, but will be included in a separate binder within the EPA format as an effort in transparency and completeness. All studies will be submitted to both agencies, even if the data is not specifically required by one of the agencies. all studies supporting this registration request, including those previously submitted, are listed in the OECD study list. EPA specific submission forms will not be included in the APVMA submission, and visa versa. Separate product labels will be submitted to EPA and APVMA, and Efficacy data will be submitted to APVMA only.

An Extension of the current EPA 'Temporary Exemption from the Requirements of a Tolerance' to a permanent exemption is being requested from both agencies, based on the natural and ubiquitous occurrence of S-ABA and it's lack of any toxicological response in the mammalian and ecological toxicity testing.

S-Abscisic Acid is a naturally occurring plant growth hormone. It is naturally synthesized, utilized and metabolized in the course of natural plant physiology. It has been found at various concentrations in all plants in which it was looked for, and it's concentration is known to naturally fluctuate quite significantly depending upon the stage and environmental conditions of the plant.

The S-Abscisic Acid 'Technical Grade Active Ingredient (TGAI)' being registered by Valent BioSciences is a natural product produced by a fermentation process. It is subsequently isolated and purified to give the Technical Grade Active Ingredient (TGAI) used in the Valent End Use products. This TGAI, being a fermentation product, is produced by an organism and therefore identical to S-ABA produced by other organism in the environment.

Valent BioSciences has performed the acute toxicity tests (acute oral, acute dermal, acute inhalation, primary eye irritation, primary skin irritation, and dermal sensitization), subchronmic toxicity tests (90-day oral repeat dose, 21-day dermal repeat dose, and 90-day inhalation repeat dose), Mutagenicity testing [Reverse Mutation; *Salmonella typhimurium* and *Escherichia coli* tester strain., *In vivo* clastogenic activity, micronuclei in polychromatic erythrocytes in CD-1 (ICR)BR mouse bone marrow, and chromosomal aberrations in cultured Chinese hamster ovary (CHO) cells], prenatal developmental toxicity, and a reporter gene assay for endocrine disruption evaluation, on the TGAI (S-Abscisic Acid). All of these studies were performed at standard limit doses and all of these studies showed no toxicity of the tested material. The only response seen in any test was a mild irritation effect in the primary eye irritation test which cleared in all animals by the end of the test.

A 21-day repeat-dermal exposure study was performed based on the pre-registration conference input received from the EPA (pre-registration conference held between Valent BioSciences and EPA on July 13, 2005). During this conference Valent BioSciences was advised to perform a 21-day repeat-exposure dermal toxicity study to support the full registration because of the potential for repeat exposure from the ornamental use pattern.

The formulated End Use Products, containing 10% or 20% active, also showed a lack of toxicity. The acute tests were performed on VBC-30051 (a 20% active solid formulation) and on VBC-30074 (a 10% active aqueous liquid formulation). The VBC-30101 product (a 10% active aqueous liquid formulation) is almost identical to the VBC-30074 formulation (with the addition of [redacted] each at less than 0.5%). The eye irritation test for VBC-30101 was performed and gave the same results as the eye irritation test for VBC-30074, demonstrating on the only test that showed any observable effect that these two formulated products are toxicologically the same.

Waivers are being requested for the additional acute toxicity testing of VBC-30101 with substitution of the test data obtained from VBC-30074 (an essentially identical formulation).

Because S-ABA is one of the major natural plant growth regulators, considerable information is present in the published literature. This literature information regarding the natural occurrence in various plants and other organisms and its concentrations, biosynthesis, metabolism and degradation, and the biochemical and physiological effects, is presented in a summary document which is accompanied by the literature articles referenced.

Acute ecological toxicity testing has been conducted by Valent BioSciences with Bobwhite quail, rainbow trout, Daphnia Magna, Honey bee (contact and oral), and earthworm all under GLP. No toxicity was observed at the limit doses for these species.

Additionally, results of similar testing performed by the TGAI manufacturer are given for a complete presentation of all information in our possession, but are not maintained to be GLP studies. The species tested by the manufacturer are; zebra fish, Italian worker bee (contact and oral), silk worm, and Japanese quail. The rates used were in many cases over 10 times higher than what was used in the GLP limit tests performed by Valent BioSciences. Similar results of low to no toxicity were seen.

Non-target plant testing (vegetative vigor and seedling emergence) was performed with the VBC-30074 formulation. No toxic effects and little overall effect were observed in these tests. Additional testing beyond the tier I level is not considered necessary and Valent BioSciences has requested a wavier from additional testing.

Because of the low acute toxicity to these species at the high limit doses used, testing with the formulations which contain only 10 to 20% active ingredient is not believed to be informative. All 'non-active' formulation ingredients are themselves not toxic and therefore the total formulation would be less toxic than what was observed for the TGAI concentrate. Because of the low acute toxicity seen at rates higher than the limit doses, and because S-ABA is already present in nature at low doses in all diets that contain plant materials, dietary studies and higher tier studies with fish, fowl or other ecological species are not believed to be informative. Valent is requesting a waiver from the requirements for this toxicity testing of the end use products.

This request for a pesticide registration is for the new biochemical active ingredient S-Abscisic Acid (VBC-30054) TGAI for manufacturing use only, and two formulations of that active (VBC-30101 a liquid concentrate formulation and VBC-30051 a soluble granule formulation), for use on ornamental and grape crops. The Product names for these formulations are; ConTego Pro® SG and ConTego Pro® SL for use on ornamentals (for VBC-30051 and VBC-30101 respectively) and ProTone® SG and ProTone® SL for use on grapes (for VBC-30051 and VBC-30101 respectively). Extension of the current 'Temporary Exemption from the Requirements of a Tolerance' to a 'Permanent Exemption from the Requirement of a Tolerance' is also being requested.

VALENT BIOSCIENCES

Valent BioSciences believes this action fits the category of B590 "New Active ingredient; Food use; establish tolerance exemption", with a cost of $26,250.00 and a PRIA timeline of 16 months. Valent BioSciences has previously submitted payment for this registration action; [Pay.gov tracking ID: 24UFQO6M, Name of account: Valent BioSciences Corp., Payment amount: $26,250.00, Payment date: Dec 31, 2007].

This EPA application is organized as follows:

Administrative Documents
- Cover Letter
- Notice of Filing

VBC-30054 (TGAI)
- Form 8570-1 Application for Pesticide Registration
- Form 8570-34 Certification with Respect to Citation of Data
- Form 8570-35 Data Matrix
- Form 8570-4 CSF (VBC-30054, Technical Material)

VBC-30051 (Soluble Granular Formulation)
- Form 8570-1 Application for Pesticide Registration
- Form 8570-34 Certification with Respect to Citation of Data
- Form 8570-35 Data Matrix
- Form 8570-4 CSF (VBC-30051, Soluble Granule)

VBC-30101 (Soluble Liquid Formulation)
- Form 8570-1 Application for Pesticide Registration
- Form 8570-34 Certification with Respect to Citation of Data
- Form 8570-35 Data Matrix
- Form 8570-4 CSF (VBC-30101 Soluble Liquid)

Transmittal Document
List of Studies by Type and Author (OECD Formatted)

Section A - Chemical and Physical Properties
Section B - Proposed Use Label,
- TGAI Label, Manufacturing Use Only
- Master Label (VBC-30051 Soluble Granule formulation)
- Master Label (VBC-30101 Soluble Liquid formulation)

Section C - Toxicology Data
Section D - Residue Summary & Residue Analytical methods
Section E - Tolerance - Tolerance Exemption

Included within this EPA application, Valent BioSciences Corp. is attaching a transmittal document that lists 43 new studies in support of this registration request.

VALENT BIOSCIENCES

Please be aware that Valent BioSciences has submitted along with the Product Use labels included in Section B, five additional copies of each label.

Please contact me at (847)-968-4726 if I can be of any assistance during the review of this application.

Sincerely.

Thomas Bade Ph.D.
Regulatory Manager
Valent BioSciences

Transmittal Document
Application for Registration of
S-Abscisic Acid (S-ABA)

Submitter: Valent BioSciences Corp.
870 Technology Way
Libertyville, IL 60048

Regulatory Action: In support of the Biochemical pesticide registration of end-use Products of S-Abscisic Acid (Natural Plant Growth regulator) for use on ornamentals (to mitigate the effects of environmental stress) and on grapes (to enhance color development).

Transmittal Date: July 7, 2008

Listing of Submitted Studies:

Document 1

Title: Analysis and Certification of Product Ingredients in Five Batches of Technical S-Abscisic Acid
Data requirements: 40 CFR § 151-13
OPPTS 830.1700
Study Date: October 18, 2007
Performing Laboratory: PTRL West, Inc.
625-B Alfred Nobel Drive
Hercules, CA 94547
Project ID: 1473W

MRID No.: _____

Document 2

Title: Product Identity Confidential Statement of Formula VBC-30101 (S-ABA, S-Abscisic Acid Liquid Formulation)
Data requirements: 40 CFR § 151-10, § 151-11, § 151-12,
OPPTS 880.1100, 880.1200, 880.1400
Study Date: January 3, 2008
Performing Laboratory: Valent BioSciences Corporation
870 Technology Way
Libertyville, IL 60048
Project ID: S-ABA 30101; 127-1

MRID No.: _____

Document 3

Title: S-Abscisic Acid: VBC-30054, Technical Powder,
Product Chemistry: Certification of Limits
Data requirements: 40 CFR § 151-15
OPPTS 830.1750
Study Date: January 3, 2008
Performing Laboratory: Valent BioSciences Corporation
870 Technology Way
Libertyville, IL 60048
Project ID: S-ABA 30101; 127-2

MRID No.: _____

Document 4

Title: Analysis of S-Abscisic Acid in Five Lots of VBC-30051 Formulation, by High Performance Liquid Chromatography
Data requirements: 40 CFR § 151-13,
Study Date: December 14, 2007
Performing Laboratory: Valent BioSciences Corp. Research Center
6131 Oakwood Road
Long Grove, IL 60047
Project ID: VBCL07-48060-07

MRID No.: _____

Document 5

Title: Analysis of S-Abscisic Acid in Five Lots of VBC-30101 Formulation, by High Performance Liquid Chromatography

Data requirements: 40 CFR § 151-13,
Study Date: February 15, 2008
Performing Laboratory: Valent BioSciences Corp. Research Center
6131 Oakwood Road
Long Grove, IL 60047
Project ID: VBCL08-48060-01

MRID No.: _____

Document 6

Title: Stability of S-Abscisic Acid Active Ingredient to Normal and Elevated Temperatures, Metals, and Metal Ions and Oxidizing Reducing Properties of S-Abscisic Acid Active Ingredient.
Data requirements: OPPTS 830.6313, 830.6314,
Study Date: September 5, 2007
Performing Laboratory: PTRL West, Inc.
625-B Alfred Nobel Drive
Hercules, CA 94547
Project ID: 1618W
PTRL Report ID: 1618W-1

MRID No.: _____

Document 7

Title: Accelerated Storage Stability of VBC-30051 at Elevated Temperatures

Data requirements: OPPTS 830.6313
Study Date: June 13, 2007
Performing Laboratory: PTRL West, Inc.
625-B Alfred Nobel Drive
Hercules, California 94547
Project ID: PTRL West # 1612W
Report ID: PTRL West # 1612W-001

MRID No.: _____

Document 8

Title: Accelerated Storage Stability of VBC-30074 at Elevated Temperatures

Data requirements: OPPTS 830.6313
Study Date: June 13, 2007
Performing Laboratory: PTRL West, Inc.
625-B Alfred Nobel Drive
Hercules, California 94547
Project ID: PTRL West # 1613W
Report ID: PTRL West # 1613W-001

MRID No.: _____

Document 9

Title: Accelerated Storage Stability of VBC-30101 at Elevated Temperatures

Data requirements: OPPTS 830.6313
Study Date: January 14, 2008
Performing Laboratory: PTRL West, Inc.
625-B Alfred Nobel Drive
Hercules, California 94547
Project ID: PTRL West # 1728W
Report ID: PTRL West # 1728W-001

MRID No.: _____

Document 10

Title: VBC-30054 Physico-Chemical Properties

Data requirements: 40 CFR § 151-10
Study Date: December 5, 2007
Performing Laboratory: Huntingdon Life Science Ltd.
Woolley Road
Alconbury, Huntingdon
Cambridgeshire PE28 4HS, England
Project ID: ZAB/0083/072858

MRID No.: _____

Document 11

Title: Solubility of S-Abscisic Acid in Organic Solvents

Data requirements: OPPTS 830.7840
Study Date: March 26, 2008
Performing Laboratory: PTRL West, Inc.
625-B Alfred Nobel Drive
Hercules, California 94547
Project ID: PTRL West # 1730W
Report ID: PTRL West # 1730W-1

MRID No.: _____

Document 12

Title: Hydrolysis of S-Abscisic Acid at pH 4, 7 and 9

Data requirements: OPPTS 835.2110
Study Date: April 24, 2008
Performing Laboratory: PTRL West, Inc.
625-B Alfred Nobel Drive
Hercules, California 94547
Project ID: PTRL West # 1729W
Report ID: PTRL West # 1729W-1

MRID No.: _____

Document 13

Title: Evaluation of the Environmental Safety of S-Abscisic Acid

Data requirements: Not Specified
Study Date: November 30, 2004
Performing Laboratory: Performing Laboratory: Nanjing Institute of Environmental Sciences, State Environmental Protection Administration of Chinese, for Sichuan Lomon Fusheng Biotechnology Co. Ltd.,

Test Number: 2004B-04

MRID No.: _____

Document 14

Title: Certification of S-ABA Reference Standards (Lot # 030806D1)

Data requirements: OPPTS 830.1550
Study Date: December 22, 2004
Performing Laboratory: Analytical Chemistry, deCODE chemistry
2501 Davey Road
Woodridge, IL 60517
Project ID: VAL0105DX
Report #: REP-RC-2004-048

MRID No.: _____

Document 15

Title: Retest of S-ABA Reference Standards (Lot # 030806D1)

Data requirements: OPPTS 830.1550
Study Date: August 4, 2005
Performing Laboratory: Analytical Chemistry, deCODE chemistry
2501 Davey Road
Woodridge, IL 60517
Project ID: VAL0107DX
Report #: REP-RC-2005-039

MRID No.: _____

Document 16

Title: VBC 30101: Supplement to Physical and Chemical Properties: Justification for Waivers from Flammability, Explodability, and Corrosion Characteristics.

Data requirements: 40 CFR, OPPTS 830.6315, 830.6316, 830.6320
Study Date: February 8, 2008
Performing Laboratory: Valent BioSciences Corporation
870 Technology Way, Suite 100
Libertyville, IL 60048
Project ID: S-ABA 30101; 127-3

MRID No.: _____

Document 17

Title: Physical Properties of VBC-30051

Data requirements: 40 CFR § 151-10
Study Date: December 5, 2007
Performing Laboratory: PTRL West, Inc.
625-B Alfred Nobel Drive
Hercules, California 94547
Project ID: PTRL West # 1614W

MRID No.: _____

Document 18

Title: Physical Properties of VBC-30074

Data requirements: 40 CFR § 151-10
Study Date: October 17, 2007
Performing Laboratory: PTRL West, Inc.
625-B Alfred Nobel Drive
Hercules, California 94547
Project ID: PTRL West # 1615W

MRID No.: _____

Document 19

Title: Physical Properties of VBC-30101

Data requirements: OPPTS 830.6302, 830.6303, 830.6304, 830.7000, 830.7100, 830.7300
Study Date: January 14, 2008
Performing Laboratory: PTRL West, Inc.
625-B Alfred Nobel Drive
Hercules, California 94547
Project ID: PTRL West # 1720W
Report ID: PTRL West # 1720W-1

MRID No.: _____

Document 20

Title: VBC-30101 Primary Eye Irritation Study in Rabbits

Data requirements: 40 CFR § 152-13, OPPTS 870.2400
Study Date: December 12, 2007
Performing Laboratory: Product Safety Laboratories
2394 Highway 130
Dayton, New Jersey 08810
Project ID: 23416

MRID No.: _____

Document 21

Title: Justification for Waiver Request from the Biochemical Pesticide Toxicity Data Requirements For Acute Oral Toxicity Testing For VBC-30101

Data requirements: 40 CFR § 152-10, OPPTS 870.1100
Study Date: January 3, 2008
Performing Laboratory: Valent BioSciences Corporation
870 Technology Way, Suite 100
Libertyville, IL 60048
Project ID: S-ABA 30101; 127-11

MRID No.: _____

Document 22

Title: Justification for Waiver Request from the Biochemical Pesticide Toxicity Data Requirements For Acute Dermal Toxicity Testing For VBC-30101

Data requirements: 40 CFR § 152-11, OPPTS 870.1200
Study Date: January 3, 2008
Performing Laboratory: Valent BioSciences Corporation
870 Technology Way, Suite 100
Libertyville, IL 60048
Project ID: S-ABA 30101; 127-12

MRID No.: _____

Document 23

Title: Justification for Waiver Request from the Biochemical Pesticide Toxicity Data Requirements For Inhalation Toxicity Testing For VBC-30101

Data requirements: 40 CFR § 152-12, OPPTS 870.1300
Study Date: January 3, 2008
Performing Laboratory: Valent BioSciences Corporation
870 Technology Way, Suite 100
Libertyville, IL 60048
Project ID: S-ABA 30101; 127-13

MRID No.: _____

Document 24

Title: Justification for Waiver Request from the Biochemical Pesticide Toxicity Data Requirements For Dermal Irritation Toxicity Testing For VBC-30101

Data requirements: 40 CFR § 152-14, OPPTS 870.2500
Study Date: January 3, 2008
Performing Laboratory: Valent BioSciences Corporation
870 Technology Way, Suite 100
Libertyville, IL 60048
Project ID: S-ABA 30101; 127-14

MRID No.: _____

Document 25

Title: Justification for Waiver Request from the Biochemical Pesticide Toxicity Data Requirements For Dermal Sensitization Toxicity Testing For VBC-30101

Data requirements: 40 CFR § 152-15, OPPTS 870.2600
Study Date: January 3, 2008
Performing Laboratory: Valent BioSciences Corporation
870 Technology Way, Suite 100
Libertyville, IL 60048
Project ID: S-ABA 30101; 127-15

MRID No.: _____

Document 26

Title: Justification for Waiver Request from the Biochemical Pesticide Toxicity Data Requirements For 90-Day Repeat Inhalation Toxicity Testing For VBC-30101

Data requirements: 40 CFR § 152-22, OPPTS 870.3465
Study Date: January 3, 2008
Performing Laboratory: Valent BioSciences Corporation
870 Technology Way, Suite 100
Libertyville, IL 60048
Project ID: S-ABA 30101; 127-16

MRID No.: _____

Document 27

Title: VBC-30054: One-Week Toxicity Dose Range Finding Study in Rats with Dermal Administration

Data requirements: OPPTS 830.7000
Study Date: January 23, 2008
Performing Laboratory: Charles River Laboratories
Tranent
Edinburgh EH33 2NE, UK
Project ID: 458194
Report No: 27954 Report Amendment 1

MRID No.: _____

Document 28

Title: VBC-30054: 3 Week Toxicity Study in Rats with Dermal Administration

Data requirements: OPPTS 830.7000
Study Date: February 1, 2008
Performing Laboratory: Charles River Laboratories
Tranent
Edinburgh EH33 2NE, UK
Project ID: 458215
Report No: 27971

MRID No.: _____

Document 29

Title: VBC-30054: 4 Week Toxicity Study in Rats with Administration by the Diet

Data requirements: 40 CFR, OPPTS 870.3100
Study Date: February 1, 2008
Performing Laboratory: Charles River Laboratories
Tranent
Edinburgh EH33 2NE, UK
Project ID: 457866
Report No: 27720

MRID No.: _____

Document 30

Title: VBC-30054: 13 Week Toxicity Study in Rats with Administration by the Diet

Data requirements: 40 CFR § 152.20, OPPTS 870.3100
Study Date: February 1, 2008
Performing Laboratory: Charles River Laboratories
Tranent
Edinburgh EH33 2NE, UK
Project ID: 457871
Report No: 28084

MRID No.: _____

Document 31

Title: VBC-30054: Preliminary Developmental Toxicity Study in Rats

Data requirements: 40 CFR § 152-23, OPPTS 870.3700
Study Date: March 21, 2008
Performing Laboratory: Charles River Laboratories
Tranent
Edinburgh EH33 2NE, UK
Project ID: 494845
Report N0.: 28566

MRID No.: _____

Document 32

Title: A Prenatal Developmental Toxicity Study of S-Abscisic Acid in Rats

Data requirements: OPPTS 870.3700, OECD 414
Study Date: May 5, 2008
Performing Laboratory: WIL Research Laboratories, LLC
1407 George Road
Ashland, OH 44805
Project ID: WIL-505004

MRID No.: _____

Document 33

Title: Reporter gene assay for abscisic acid (ABA) using human estrogen and androgen receptors

Data requirements: 40 CFR § 152-24, OPPTS 870.3700
Study Date: December 14, 2007
Performing Laboratory: Environmental Health Science Laboratory
Sumitomo Chemical Co., Ltd.
1-98, 3-chome
Kasugade-Naka
Konohana-Ku
Osaka, Japan
Project No.: VBC-SCC ABA 12-14-07

MRID No.: _____

Document 34

Title: Abscisic Acid: An Acute Toxicity Study With the Earthworm In An Artificial Soil Substrate

Data requirements: OECD Guideline 207
Study Date: March 12, 2008
Performing Laboratory: Wildlife International, Ltd.
8598 Commerce Drive
Easton, Maryland 21601, USA
Project ID: 529-119

MRID No.: _____

Document 35

Title: Environmental Safety Assessment of Natural Abscisic Acid

Data requirements: Not Specified
Study Date: June 25, 2000
Performing Laboratory: Performing Laboratory: Nanjing Institute of Environmental Sciences, State Environmental Protection Administration of Chinese, for Sichuan Lomon Fusheng Biotechnology Co. Ltd..
Test Number: June 2000

MRID No.: _____

Document 36

Title: VBC-30074: A Toxicity Test to Determine the Effects of The Test Substance on Vegetative Vigor of Ten Species of Plants

Data requirements: OPPTS 850.4150
Study Date: April 2, 2008
Performing Laboratory: Wildlife International, Ltd.
8598 Commerce Drive
Easton, Maryland 21601, USA
Project ID: 529-115

MRID No.: _____

Document 37

Title: VBC-30074: A Toxicity Test to Determine the Effects of The Test Substance on Seedling Emergence of Ten Species of Plants

Data requirements: OPPTS 850.4100
Study Date: April 2, 2008
Performing Laboratory: Wildlife International, Ltd.
8598 Commerce Drive
Easton, Maryland 21601, USA
Project ID: 529-116

MRID No.: _____

Document 38

Title: Background of Abscisic Acid (ABA) A Plant Growth Regulator for use on Grapes and Ornamentals

Data requirements: Background Information, Summary of Published Literature
Study Date: May 23, 2008
Performing Laboratory: Valent BioSciences Corp. Research Center
6131 Oakwood Road
Long Grove, IL 60047
Project ID: ABA – LS2

MRID No.: _____

Document 39

Title: Copies of Referenced Papers in 'Background of Abscisic Acid (ABA) A Plant Growth Regulator for use on Grapes and Ornamentals'

Data requirements: Background Information, Summary of Published Literature
Study Date: May 29, 2008
Performing Laboratory: Valent BioSciences Corp. Research Center
6131 Oakwood Road
Long Grove, IL 60047
Project ID: ABA – LS2 REF

MRID No.: _____

Document 40

Title: Characterization of the 1'-4'-*trans*-diol of Abscisic Acid Reference Standard (VBC-30084)

Data requirements: 40 CFR 160.105(a) Test, Control and References Substances Characterization
Study Date: March 30, 2007
Performing Laboratory: Valent BioSciences Corp. Research Center
6131 Oakwood Road
Long Grove, IL 60047
Project ID: VBCL07-48060-01

MRID No.: _____

Document 41

Title: Abscisic Acid (S-ABA) Request for a waiver from the Biochemical Pesticide Registration Requirements for Avian Dietary Toxicity Testing

Data requirements: OPPTS 850.2200
Study Date: May 30, 2008
Performing Laboratory: Valent BioSciences Corp.
870 Technology Way
Libertyville, IL 60048
Project ID: S-ABA 30054: 058-1

MRID No.: _____

Document 42

Title: Abscisic Acid (S-ABA) Request for a waiver from the Biochemical Pesticide Registration Requirements for Multi Residue Testing Method

Data requirements: OPPTS 860.1360

Study Date: May 30, 2008
Performing Laboratory: Valent BioSciences Corp.
870 Technology Way
Libertyville, IL 60048
Project ID: S-ABA 30054; 058-2

MRID No.: _____

Document 43

Title: S-Abscisic Acid (S-ABA), ProTone® SG, "Australian efficacy data S-ABA use on Grapes"

Data requirements: NA

Study Date: July, 2008
Performing Laboratory: Valent BioSciences
A Division of Sumitomo Chemical Australia Pty Ltd.

Project ID: Australian Efficacy – Grape Use

MRID No.: _____

Company Official: 7/7/08
Signature

Company Name: Valent BioSciences Corporation

Company Contact: Thomas Bade Ph.D. 847-968-4726
Regulatory Manager Phone

Form Approved OMB Nos. 2070-0060; 2070-0057; 2070-0107; 2070-0122; 2070-0164

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
1200 Pennsylvania Avenue, N.W.
WASHINGTON, D.C. 20460

Paperwork Reduction Act Notice: The public reporting burden for this collection of information is estimated to average 1.25 hours per response for registration and 0.25 hours per response for reregistration and special review activities, including time for reading the instructions and completing the necessary forms. Send comments regarding burden estimate or any other aspect of this collection of information, including suggestions for reducing the burden to: Director, Collection Strategies Division (2822T), U.S. Environmental Protection Agency, 1200 Pennsylvania Avenue, N.W., Washington, DC 20460. Do not send the completed form to this address.

Certification with Respect to Citation of Data

Applicant's/Registrant's Name, Address, and Telephone Number Valent BioScineces Corp. 870 Technology Way, Libertyville, IL 60048	EPA Registration Number/File Symbol 73049-XX
Active Ingredient(s) and/or representative test compound(s) VBC-30054 (S-Abscisic Acid) Technical Grade Active Ingredient	Date June 9, 2008
General Use Pattern(s) (list all those claimed for this product using 40 CFR Part 158) For Manufacturing Use Only	Product Name S-Abscisic Acid

NOTE: If your product is a 100% repackaging of another purchased EPA-registered product labeled for all the same uses on your label, you do not need to submit this form. You must submit the Formulator's Exemption Statement (EPA Form 8570-27).

☐ I am responding to a Data-Call-In Notice, and have included with this form a list of companies sent offers of compensation (the Data Matrix form should be used for this purpose).

SECTION I: METHOD OF DATA SUPPORT (Check one method only)

☐ I am using the cite-all method of support, and have included with this form a list of companies sent offers of compensation (the Data Matrix form should be used for this purpose).

☐ I am using the selective method of support (or cite-all option under the selective method), and have included with this form a completed list of data requirements (the Data Matrix form must be used).

SECTION II: GENERAL OFFER TO PAY

[Required if using the cite-all method or when using the cite-all option under the selective method to satisfy one or more data requirements]

☐ I hereby offer and agree to pay compensation, to other persons, with regard to the approval of this application, to the extent required by FIFRA.

SECTION III: CERTIFICATION

I certify that this application for registration, this form for reregistration, or this Data-Call-In response is supported by all data submitted or cited in the application for registration, the form for reregistration, or the Data-Call-In response. In addition, if the cite-all option or cite-all option under the selective method is indicated in Section I, this application is supported by all data in the Agency's files that (1) concern the properties or effects of this product or an identical or substantially similar product, or one or more of the ingredients in this product; and (2) is a type of data that would be required to be submitted under the data requirements in effect on the date of approval of this application if the application sought the initial registration of a product of identical or similar composition and uses .

I certify that for each exclusive use study cited in support of this registration or reregistration, that I am the original data submitter or that I have obtained the written permission of the original data submitter to cite that study.

I certify that for each study cited in support of this registration or reregistration that is not an exclusive use study, either: (a) I am the original data submitter; (b) I have obtained the permission of the original data submitter to use the study in support of this application; (c) all periods of eligibility for compensation have expired for the study; (d) the study is in the public literature; or (e) I have notified in writing the company that submitted the study and have offered (i) to pay compensation to the extent required by sections 3(c)(1)(F) and/or 3(c)(2)(B) of FIFRA; and (ii) to commence negotiations to determine the amount and terms of compensation, if any, to be paid for the use of the study.

I certify that in all instances where an offer of compensation is required, copies of all offers to pay compensation and evidence of their delivery in accordance with sections 3(c)(1)(F) and/or 3(c)(2)(B) of FIFRA are available and will be submitted to the Agency upon request. Should I fail to produce such evidence to the Agency upon request, I understand that the Agency may initiate action to deny, cancel or suspend the registration of my product in conformity with FIFRA.

I certify that the statements I have made on this form and all attachments to it are true, accurate, and complete. I acknowledge that any knowingly false or misleading statement may be punishable by fine or imprisonment or both under applicable law.

Signature	Date	Typed or Printed Name and Title
Thomas Bade	6/9/08	Thomas Bade, Regulatory Manager

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Form Approved OMB No. 2070-0060

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
401 M Street, S.W.
WASHINGTON, D.C. 20460

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DATA MATRIX

Date June 9, 2008	EPA Reg No./File Symbol 73049-	Page 1 of 5
Applicant's/Registrant's Name & Address Valent BioSciences Corporation, 870 Technology Way, Livertyville, IL, 60048	Product VBC-30054 (S-Abscisic Acid); TGAI for Manufacturing Use Only	

Ingredient S-Abscisic Acid (S-ABA); (S)-5-(1-hydroxy-2,6,6-trimethyl-4-oxo-2-cyclohexen-1-yl)-3-methyl-(2Z,4E)-pentadienoic acid, [CAS # 21293-29-8]

Guideline Reference Number	Guideline Study Name	MRID Number	Submitter	Status	Note
880.1100, 880.1200, 880.1400	Integrated Manufacturing Process S-ABA # 30054; 056-4	46895601	Valent BioSciences EPA # 73049	OWN	
880.1100, 880.1200, 880.1400	Integrated Manufacturing Process S-ABA # 30054; 027-1	47067903	Valent BioSciences EPA # 73049	OWN	
830.1700, 830.1750, 830.1800	Product Chemistry: Analysis, Cert limits, # 30054; 056-5	46895602	Valent BioSciences EPA # 73049	OWN	
830.1700, 830.1750, 830.1800	Product Chemistry; Analysis, Cert limits, # 30054; 027-2	47067904	Valent BioSciences EPA # 73049	OWN	
830.1700	Technical 5-Lot Analysis, PTRL # 1473W		Valent BioSciences EPA # 73049	OWN	
830.1700	VBC-30054 Product Chem: Cert Limits # 30054; 127-2		Valent BioSciences EPA # 73049	OWN	
830.1800	Anal Mtd; Validation TGAI and formulation, PTRL# 1442W	46895610	Valent BioSciences EPA # 73049	OWN	
830.1700	Charaterization of 1-4 diol # VBCL07-48060-01		Valent BioSciences EPA # 73049	OWN	
830.0000	30054 Phys Chem Summary, # 30054; 056-3	46895603	Valent BioSciences EPA # 73049	OWN	
830.6302, 830.6303, 830.6304	30054 Phys Cehm Characteristics PRTL # 1438W	46895604	Valent BioSciences EPA # 73049	OWN	
830.6313	30054 Stability, Temp, Metals & Ions PTRL # 1618W-1		Valent BioSciences EPA # 73049	OWN	
830.6315	30054 Flamability, Explodability, HLS # ZAB0083/072858		Valent BioSciences EPA # 73049	OWN	
830.7000, 830.7300	30054 pH, PTRL # 1558W	46895607	Valent BioSciences EPA # 73049	OWN	
830.7200, 830.7300	30054 Melting Point, Density PTRL # 1438W	46895604	Valent BioSciences EPA # 73049	OWN	
830.7840, 7550, 7560, 7570	30054 water Sol, Part Coef, Diss Const, PTRL#1437W	46895605	Valent BioSciences EPA # 73049	OWN	

Signature Thomas Bade	Name and Title Thomas Bade, Regulatory Manager	Date 6/9/08

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DATA MATRIX

Date June 9, 2008	EPA Reg No./File Symbol 73049-	Page 2 of 5
Applicant's/Registrant's Name & Address Valent BioSciences Corporation, 870 Technology Way, Livertyville, IL, 60048	Product VBC-30054 (S-Abscisic Acid); TGAI for Manufacturing Use Only	

Ingredient S-Abscisic Acid (S-ABA); (S)-5-(1-hydroxy-2,6,6-trimethyl-4-oxo-2-cyclohexen-1-yl)-3-methyl-(2Z,4E)-pentadienoic acid, [CAS # 21293-29-8]

Guideline Reference Number	Guideline Study Name	MRID Number	Submitter	Status	Note
830.0000	Lomon Phys Chem Summary # 2004B-04		Valent BioSciences EPA # 73049	OWN	
830.1800	Analytical HPLC Method # VBC-M04001.2		Valent BioSciences EPA # 73049	OWN	
830.7050	30054 - UV/Vis Abs, Spectra DeCode REP-RC-2004-048		Valent BioSciences EPA # 73049	OWN	
830.7050	30054 - Ref Std retest DeCode REP-RC-2005-039		Valent BioSciences EPA # 73049	OWN	
830.7950	30054 - Vapour Pressure, PTRL # 1436W-1	46895606	Valent BioSciences EPA # 73049	OWN	
830.7840	30054 - Solubility in Organic Solvents, PTRL # 1730W-1		Valent BioSciences EPA # 73049	OWN	
830.2110	30054 - Hydrolysis at pH 4, 7, 9, PTRL # 1729W-1		Valent BioSciences EPA # 73049	OWN	

Signature Thomas Bade	Name and Title Thomas Bade, Regulatory Manager	Date 6/9/08

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DATA MATRIX

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Applicant's/Registrant's Name & Address Valent BioSciences Corporation, 870 Technology Way, Libertyville, IL, 60048	Product VBC-30054 (S-Abscisic Acid); TGAI for Manufacturing Use Only	

Ingredient S-Abscisic Acid (S-ABA); (S)-5-(1-hydroxy-2,6,6-trimethyl-4-oxo-2-cyclohexen-1-yl)-3-methyl-(2Z,4E)-pentadienoic acid, [CAS # 21293-29-8]

Guideline Reference Number	Guideline Study Name	MRID Number	Submitter	Status	Note
870.1100	30054 - Acute Oral, PSL # 16974	46895611	Valent BioSciences EPA # 73049	OWN	
870.1200	30054 - Acute Dermal, PSL # 16975	46895612	Valent BioSciences EPA # 73049	OWN	
870.1300	30054 - Acute Inhalation, PSL # 17515	46895613	Valent BioSciences EPA # 73049	OWN	
870.2400	30054 - Primary Eye Irriation, PSL # 16976	46895614	Valent BioSciences EPA # 73049	OWN	
870.2500	30054 - Primary Dermal Irritation, PSL # 16977	46895615	Valent BioSciences EPA # 73049	OWN	
870.2600	30054 - Dermal Sensitization, PSL # 16978	46895616	Valent BioSciences EPA # 73049	OWN	

Signature	Name and Title	Date
Thomas Bade	Thomas Bade, Regulatory Manager	6/9/08

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Ingredient S-Abscisic Acid (S-ABA); (S)-5-(1-hydroxy-2,6,6-trimethyl-4-oxo-2-cyclohexen-1-yl)-3-methyl-(2Z,4E)-pentadienoic acid, [CAS # 21293-29-8]

Guideline Reference Number	Guideline Study Name	MRID Number	Submitter	Status	Note
870.3100	90-Day Oral Toxicity, CRL # 28084		Valent BioSciences EPA # 73049	OWN	
870.3250	21-Day Repeat Dermal, CRL # 27971		Valent BioSciences EPA # 73049	OWN	
870.3700	Teratology. preliminary Prenatal Dev, CRL # 28566		Valent BioSciences EPA # 73049	OWN	
870.3700	Teratology, Prenatal Development, # WIL-505004		Valent BioSciences EPA # 73049	OWN	
870.5100	Bacterial Reverse Mutation, Covance # 7194-101	47030901	Valent BioSciences EPA # 73049	OWN	
870.5300	In vitro cell gene mutation, Covance # 7194-103	47005301	Valent BioSciences EPA # 73049	OWN	
870.5375	In vitro cell gene mutation, Covance # 7194-102	47005302	Valent BioSciences EPA # 73049	OWN	
870.3050	4-week Oral Toxicity, CRL # 27720		Valent BioSciences EPA # 73049	OWN	
870.3100	13-Week Oral Toxicity, CRL # 28084		Valent BioSciences EPA # 73049	OWN	
N/A	Endocrine Disruptor Testing, #VBC-SCC ABA 12-14-07		Valent BioSciences EPA # 73049	OWN	

Signature Thomas Bade

Name and Title Thomas Bade, Regulatory Manager

Date 6/9/08

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DATA MATRIX

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Applicant's/Registrant's Name & Address Valent BioSciences Corporation, 870 Technology Way, Livertyville, IL, 60048	Product VBC-30054 (S-Abscisic Acid); TGAI for Manufacturing Use Only	

Ingredient S-Abscisic Acid (S-ABA); (S)-5-(1-hydroxy-2,6,6-trimethyl-4-oxo-2-cyclohexen-1-yl)-3-methyl-(2Z,4E)-pentadienoic acid, [CAS # 21293-29-8]

Guideline Reference Number	Guideline Study Name	MRID Number	Submitter	Status	Note
850.2100	Acute Avian - 30054, WI # 529-111	47067901	Valent BioSciences EPA # 73049	OWN	
850.2200	Avian Dietary tox. Waiver S-ABA 30054: 058-1		Valent BioSciences EPA # 73049	OWN	
850.1075	Acute Fish - 30054, WI # 529A-104	47131402	Valent BioSciences EPA # 73049	OWN	
850.1010	Acute invertebrate, fresh water - 30054, WI # 529A-103	47131401	Valent BioSciences EPA # 73049	OWN	
850.4100, 850.4150	Non-target plant toxicity, S-ABA 30054;047-02	47131404	Valent BioSciences EPA # 73049	OWN	
850.4100, 850.4150	Non-target plant toxicity, S-ABA 30054;047-02REF	47153201	Valent BioSciences EPA # 73049	OWN	
850.4350	Non-target Insect-honeybee, EuGAB#20071029/S1BLEU	47151201	Valent BioSciences EPA # 73049	OWN	
N/A	EarthWorm Toxicity. WI # 529-119		Valent BioSciences EPA # 73049	OWN	
850.0000	Lomon Summary of EcoTox Results, # June 2000		Valent BioSciences EPA # 73049	OWN	
850.0000	Background Review of Literature, # ABA-LS2		Valent BioSciences EPA # 73049	OWN	
850.0000	Copies of background literture papers, # ABA-LS2 REF		Valent BioSciences EPA # 73049	OWN	
860.1500	Residue Analytical method, # S-ABA 30054; 106-1	46985604	Valent BioSciences EPA # 73049	OWN	
850.1500	Fate in Grapes, resdiue Levels, # S-ABA 30025; 086-1	47005303	Valent BioSciences EPA # 73049	OWN	
860.1360	Multiresidue method testing Waiver, S-ABA 30054; 058-2		Valent BioSciences EPA # 73049	OWN	

Signature Thomas Bade	Name and Title Thomas Bade, Regulatory Manager	Date 6/9/08

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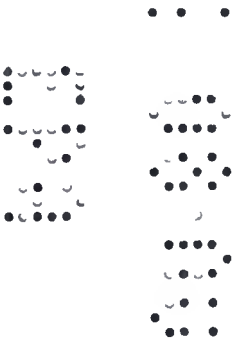
S-Abscisic Acid, (S-ABA)

(VBC-30054)
Plant Growth Regulator
Technical Grade Active Ingredient
S-Abscisic Acid (99%)

Active Ingredient	
S-Abscisic Acid	99.3% w/w
Other Ingredients	0.7% w/w
Total	100.0% w/w

KEEP OUT OF REACH OF CHILDREN
CAUTION

EPA Registration No. 73049-xx
EPA Establishment No.



Permittee:
Valent BioSciences Corporation
870 Technology Way
Libertyville, IL 60048
1-847-968-4700

Net Weight:

FIRST AID	
If in eyes	• Hold eye open and rinse slowly and gently with water for 15-20 minutes. • Remove contact lenses, if present, after the first 5 minutes, then continue rinsing eye. • Call a poison control center or doctor for treatment advice.
HOT LINE NUMBER	
Have the product container or label with you when calling a poison control center or doctor, or going for treatment. You may also call toll-free 1-800-892-0099 (24 hours) for emergency medical treatment and/or transport emergency information. For all other information, call 1-847-968-4700.	

PRECAUTIONARY STATEMENTS

HAZARDS TO HUMANS & DOMESTIC ANIMALS

CAUTION: Causes moderate eye irritation. Avoid contact with eyes or clothing. Wash thoroughly with soap and water after handling and before eating, drinking, chewing gum, using tobacco or using the toilet.

User Safety Recommendations

Users should:

- Wash hands before eating, drinking, chewing gum, using tobacco or using the toilet
- Remove clothing/PPE immediately if pesticide gets inside. Then wash thoroughly and put on clean clothing.
- Remove PPE immediately after handling this product. As soon as possible, wash thoroughly and change into clean clothing.

ENVIRONMENTAL HAZARDS

Do not apply directly to water, or to areas where surface water is present or to intertidal areas below the mean high water mark. Do not contaminate water when disposing of equipment wash-water or rinsate.

DIRECTIONS FOR USE

It is a violation of Federal law to use this product in a manner inconsistent with its label. For any requirements specific to your State or Tribe, consult the State or Tribal agency responsible for pesticide regulation.